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SEPTEMBER, 1928

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, Jan. 20, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in the Act of Feb. 28, 1925, authorized Jan. 27, 1926.

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ARCHIVES OF PATHOLOGY

VOLUME 6 SEPTEMBER, 1928 NUMBER 3

CAVERNOMATOUS TRANSFORMATION OF THE PORTAL VEIN

ITS RELATION TO BANTI'S DISEASE *

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NEW YORK

The term cavernomatous or cavernous transformation of the portal vein has been applied to a pathologic condition of the vein and the lesser omentum whereby these structures present a peculiar spongy appearance. This is due to the fact that numerous fine blood channels, instead of the portal vein, penetrate the thickened ligament. That the condition is not common is evidenced by the fact that a thorough search of the literature failed to reveal more than twenty-two cases.[1] There is a fair agreement among the writers regarding the anatomic picture, but they disagree as to the pathogenesis. The infrequency of the condition sufficiently justifies the report of a new observation, especially as the American and English literature does not contain a single instance. The case which I will report, moreover, presented several features which are of more general interest and which appear to throw some light on at least one of the groups of cases placed in the category of Banti's disease.

REPORT OF CASE

History.—J. G., a white woman, aged 35, married, who had had three children, and one miscarriage in second month, was admitted to Mount Sinai Hospital, Oct. 18, 1920. Her chief complaint was pain in the left upper quadrant which was of two years' duration. At the time of the influenza epidemic, twenty-three months before admission to the hospital, she was told she had a large spleen. Six years before she had gastric disturbance for four months. She had had measles in childhood. Six days before admission her abdomen and legs began to swell and she had pains all over the abdomen. Jaundice and tarry stools were not observed. Examination revealed an enlarged heart, and a continuous systolic and diastolic murmur, best heard to the left of the sternum and transmitted to the apex. The abdomen had a circumference of 88 cm. at the level of the umbilicus. The spleen was palpable 11 cm. below the costal margin in the midline, and the anterior edge was 7 cm. to the left of the median line. The liver was palpable at the costal

* From the Laboratories of Mount Sinai Hospital.

* Presented before the New York Pathological Society, Dec. 8, 1927.

1. The casual remarks of the following authors concerning their own observations are not included. Kaufmann: Lehrbuch der speciellen pathologischen Anatomie, ed. 7 and 8, 1922, vol. 1. Beneke, R., in Marchand-Krehl: Handbuch der allgemeine Pathologie, Leipzig, S. Hirzel, 1913, vol. 2. Benda, C., in Lubarsch-Henke: Handbuch der speciellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 2.

margin. There was moderate clubbing of the fingers. An examination of the blood made the next day gave the following results: coagulation time, six minutes; hemoglobin, 60 per cent; red blood cells, 3,750,000; white blood cells, 4,800; polymorphonuclear leukocytes, 77 per cent; basophils, 1 per cent; eosinophils, 1 per cent; lymphocytes, 20; mononuclears, 1 per cent; blood platelets, 208,000.

During a period of rest in bed the patient lost 7½ pounds (3.4 Kg.) within a week, the abdominal circumference dropped to 78 cm. and there was no more shifting dulness in the flanks. The case was diagnosed as splenic anemia in the first stage, and splenectomy was advised; it was performed on November 20 by Dr. A. A. Berg. At operation the spleen was found adherent to the diaphragm, stomach and colon. The postoperative course was stormy. A full account of the patient's condition can be found in Dr. N. Rosenthal's[2] report of case 10, in his paper on Banti's disease. The important points were as follows: There was a rapid increase in the number of platelets to 1,200,000 on the tenth day. On the twelfth day there was a sudden drop in the platelet count, followed the next day by a marked distention and considerable pain in the abdomen. Some old blood was found in the enema return, and the possibility of a thrombosis of the mesenteric veins was considered. One month later the number of blood platelets again had risen to more than 1,000,000, when there was a sudden collapse and epigastric pain. The number of blood platelets dropped to 200,000. Again a diagnosis of abdominal thrombosis was made. Later the left external jugular vein, and within a few days the right internal saphenous vein, were found to be thrombosed. After the gradual recession of the thrombosis the blood platelets began to rise. But there were other attacks of thrombosis always accompanied by a drop of blood platelets until three months after the operation. The patient was discharged and felt improved until two years later, when she complained of abdominal pain. An examination of the blood at that time showed that the platelets numbered between 1,020,000 and 1,780,000.

Course.—On Aug. 6, 1927, the patient was readmitted to the ward. She stated that for several years she had been troubled with recurrent ascites and loss of appetite. She was losing weight and getting progressively weaker. She also had noticed dyspnea and palpitation of the heart on the slightest exertion. Six days before, in the afternoon, the patient suddenly vomited; the vomitus consisted almost entirely of frank blood. These hemorrhages had recurred twice before admission. They were slightly relieved by powders and ice over the chest and abdomen.

On examination, the patient appeared to be poorly nourished; she showed a marked pallor and no jaundice. Her lips were cyanotic; she had murmurs over the enlarged heart. There was a fluid wave in the flanks; the liver was palpable two fingers' breadth below the costal margin.

Examination of the blood showed hemoglobin, 20 per cent; red blood cells, 1,300,000; white blood cells, 16,200; polymorphonuclear leukocytes, 84 per cent; lymphocytes, 15 per cent; mononuclears, 1 per cent; clotting time, six minutes; bleeding time, six minutes; platelets, 500,000; Wassermann reaction, negative; Van den Bergh reaction, negative, direct—indirect, 1 : 500,000.

A diagnosis of Banti's disease, with severe anemia and ascites, was made, and a transfusion was performed. After 240 cc. of blood was given by Unger's transfusion method the patient became suddenly restless, cyanotic and apneic; the pulse was imperceptible. Transfusion was stopped, and the patient reacted after cardiac stimulation but died shortly after. Autopsy was performed a few hours after death.

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2. Rosenthal, N.: Clinical and Hermatologic Studies on Banti's Disease, J. A. M. A. **84**:1887 (June 20) 1925.

Protocol of Autopsy.—General: The skin was pale. Edema and jaundice were not observed. Within the right antecubital fossa there was a fresh puncture mark from blood transfusion and above the right patella there was an irregularly outlined blood extravasation. Both breasts were poorly developed; the hair distribution and growth was normal. A few glands in the left axilla and in the right groin were palpable. An old transverse operative scar extended from the left middle axillary line to a point in the midline half way between the processus xyphoides and the umbilicus. It measured 19 cm.

Abdominal Cavity: The panniculus adiposus was well developed. The musculature was brown and poor. The abdominal cavity contained clear yellow fluid.[3] The visceral and parietal peritoneum was smooth. The greater omentum adhered to the lateral abdominal wall in the region of the operative scar and showed markedly distended veins. The splenic flexure of the colon was bound down to the former bed of the spleen by dense adhesions.

Lung: The left pleural cavity was empty. The left lung was slightly adherent to the thoracic wall and the diaphragm. It weighed 545 Gm. The lower lobe was not aerated. The lung was hyperemic and edematous on section. Purulent exudate escaped from the bronchial lumen on pressure. The lumina of the pulmonary artery branches were plugged by grayish-pink blood clots. The right pleural cavity was empty. The right pleura showed a few old fibrous adhesions. The right lung weighed 510 Gm. There was an old scar within the apex of the upper lobe. On section, the lung was found to be hyperemic and edematous, and it presented the same picture as the left. Trachea and bronchi contained a large amount of frothy fluid and purulent exudate. A calcified lymph node was found within the bifurcation.

Heart: The pericardial sac contained a small amount of clear yellow fluid. The epicardium was smooth and glistening. The heart weighed 300 Gm. It was not contracted. The left ventricle contained a small amount of fluid blood and was distended. The wall of the right ventricle was about 0.5 cm. thick; the papillary muscles were prominent. The valves were without changes. The coronary arteries were patent, and their intima was smooth. The heart muscle was brownish gray and easily torn. The aorta was elastic. The intima was smooth. The pulmonary artery was filled with wormlike thrombi which obstructed the lumen. The inferior vena cava was empty. Within its intrahepatic portion near the ostium of the lowest hepatic vein a thrombus adhered to the wall.

Portal Vein and Tributaries: The spleen was absent. In its place was scar tissue, and and the omentum was adherent. Beneath the splenic artery the splenic vein was found. It was narrow and received branches from the pancreas. Other tributaries from the stomach or the omentum were not conspicuous. On cross section, made about half way in its course, the lumen appeared to be divided into two narrow lumina by a septum. Proximally the lumen became narrower and was finally completely occluded. Instead of the vessel a fibrous cord was found which ended with numerous fine ramifications. An attempt to localize the portal vein failed. The superior and inferior mesenteric vein could not be identified. Instead of one large blood vessel, numerous smaller branches were seen coming from the radix of the mesentery and surrounding the superior mesenteric artery. The lateral part of the lesser omentum appeared as a fibrous fleshy plate about 1 cm. thick. The common bile duct at the lateral right edge was wide and easily probed. The hepatic artery was wide, and its wall thick. A search for the portal

3. Owing to limitation in the autopsy permit an exact measure of the fluid could not be taken.

veins at the site of the anatomic origin at the head of the pancreas failed to disclose a large patent vessel. The surface of the lesser omentum showed a network of fine blood vessels, and on cross section a great number of small lumina producing a spongy appearance were found (fig. 1). Near to the surface was seen an oval shaped blood vessel (*VP*, fig. 1) the lumen of which was completely filled with grayish-pink tissue perforated by two small lumina. It was surrounded by numerous small vascular lumina which also surrounded the hepatic artery and the common bile duct. On several sections through the lesser omentum an identical spongy or cavernous appearance was noticeable. However, the large blood vessel with the obliterated lumen could not be found in the portions more distant from the hilum of the liver. Ramifications of the portal vein were not found, and the cavernous tissue extended into the liver for about 1 cm. behind the hilum.

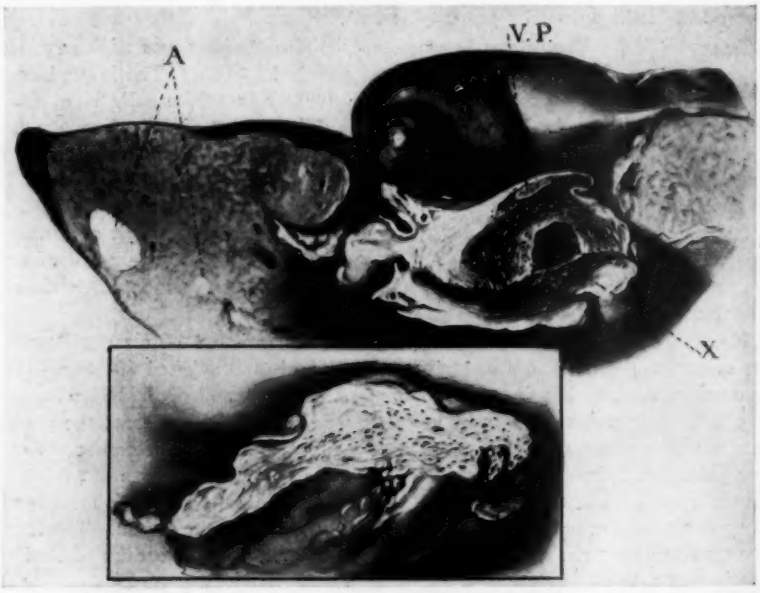

Fig. 1.—The hilum of the liver with the thickened lesser omentum perforated by numerous lumina. *V. P.* indicates obliterated portal vein; *A*, adenomas of right lobe; *X*, artefact. Small left hand drawing shows a cross section of the lesser omentum further distal. The portal vein cannot be recognized grossly.

Liver: This organ weighed 1,500 Gm. The left lobe was considerably smaller than normal and ended laterally as a thin tongue-like appendix with numerous smalll light yellow nodules. Numerous nodes of various size slightly projected on the surface of the right lobe. The largest was 20 mm. in diameter. Most of them were yellow, occasionally green, and they did not show umbilication. On section, they appeared to be liver tissue composed of large lobules. The liver was pale brown and showed on section regular lobulation. The gallbladder contained green bile.

Pancreas: The pancreas was of normal appearance. The suprarenal glands showed a narrow cortex. On the left side there were multiple vascularized adhesions between the suprarenal tissue and the bed of the spleen.

Kidneys: The left kidney weighed 150 Gm. It was normal in shape. The capsule stripped easily, revealing a smooth surface. On section, the cortical mark-

ings were distinct; the color was brown. Changes were not seen in the renal pelvis. The inferior branch of the renal vein was filled with an organized thrombus. A large branch ran upward toward the diaphragm. The right kidney weighed 150 Gm. With the exception of a few cortical cysts, it was identical with the left kidney. The bladder contained a small amount of urine.

Uterus and Adnexa: The uterus was slightly enlarged and contained some blood. The endometrium was smooth. The right ovary was wrinkled and contained a follicular cyst. The left ovary showed a less wrinkled surface and more parenchyma than the right.

Gastro-Intestinal Tract: The esophagus showed numerous markedly distended veins. Its mucosa was pale. In addition, the veins on the outside of the esophagus showed marked dilatation. The stomach contained a small amount of chyme.

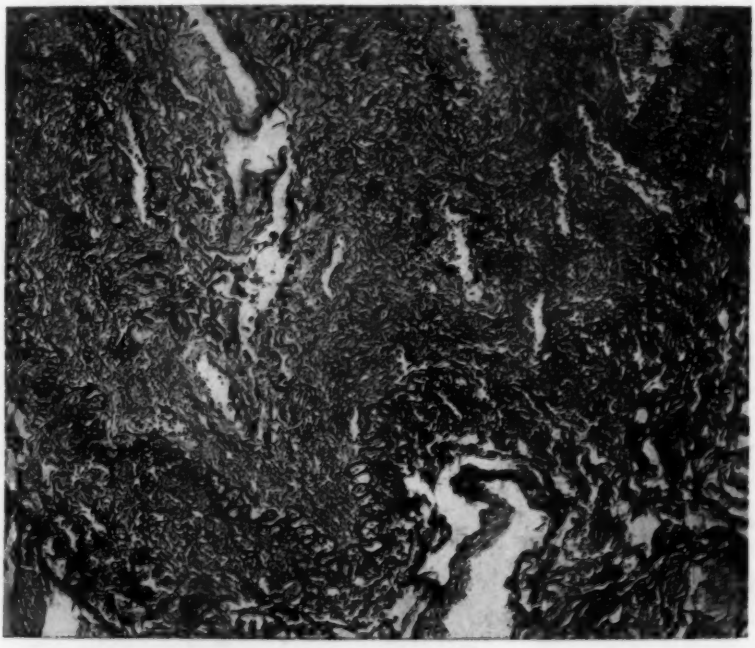

Fig. 2.—Weigert's elastica stain of the portal vein showing the sharply outlined internal elastic layer.

Throughout the stomach, especially in the cardia, the veins were markedly distended. The folds of the mucosa were red. Along the lesser curvature several superficial ulcerations were found, one of which was apparently caused by the pressure of a distended vein. Immediately beneath the pylorus there was a deep funnel-shaped ulcer, with a central thrombosed blood vessel. The jejunum contained mushy feces, the mucosa was pink. The ileum, cecum and ascending colon did not show changes. The transverse and descending colon showed congested blood vessels. The smaller venous branches of the mesocolon contained thrombi. Many of the retroperitoneal lymph nodes were red.

The neck and head were not inspected.

Diagnosis: Embolism of pulmonary artery and branches; cavernous transformation of portal vein; organized thrombosis of splenic vein and branch of left

renal vein; dilatation of the gastro-esophageal veins; multiple superficial ulcers of the stomach; chronic peptic ulcer of the duodenum; multiple adenomas of the liver; diffuse chronic purulent bronchitis; hypertrophy of the right ventricle; calcification of the tracheal lymph nodes; status after splenectomy seven years previously.

Microscopic Examination.—A section of the lesser omentum with the portal vein showed that the latter was completely filled by a coarse fibrillar connective

Fig. 3.—Splenic vein with organized and recanalized thrombus. The sharp limitation of the internal elastic layer should be noted. Evidence of endophlebitis is not seen.

tissue penetrated by multiple blood vessels. The internal elastic layer was a sharply outlined, single, wavy band (fig. 2). In a few places it was pierced by blood vessels extending from outside into the lumen. A separate intimal layer could not be recognized because the lumen was entirely filled with connective tissue attached to the elastic layer. External to this there was a narrow circular layer of

smooth muscle, reinforced by elastic fibers. The adventitial layer was wide and composed of many bundles of smooth muscle and less connective tissue, with few elastic fibers. So far, the wall of the portal vein was entirely normal. The vascular spaces which canalized the obliterated lumen were mostly compressed, and they varied in size. Some were small and lined by a layer of flat endothelial cells; some had a smooth, muscular wall. A separate, distinct elastic layer was always absent, but a fine network of elastic fibers was occasionally found separating the muscular layer from the surrounding connective tissue. Many more blood vessels of various calibers were found within the media and adventitia. The portal vein was embedded within the thickened omentum composed of connective tissue and fat. It contained many blood vessels, in some areas so densely arranged that it resembled a cavernoma. The blood channels had a muscular wall with an outer

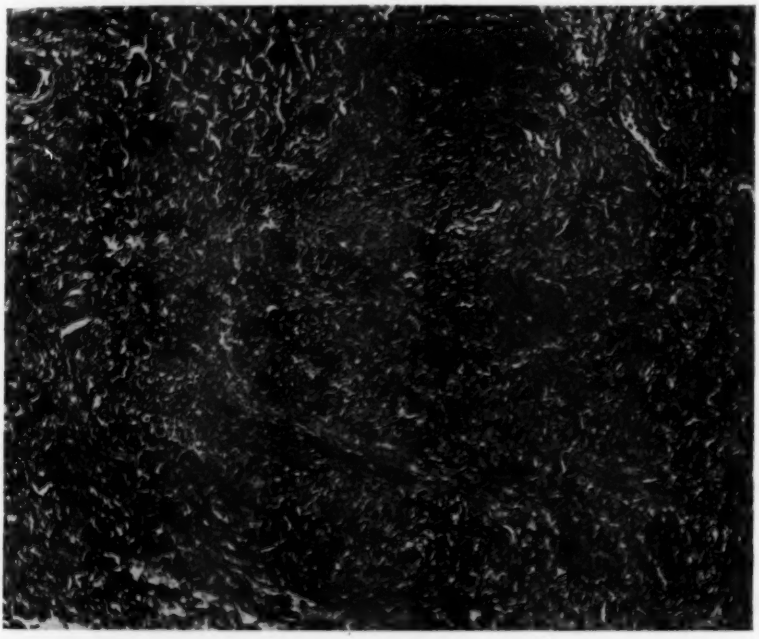

Fig. 4.—A section from the hilum of the spleen; obliterated vein. The sharply outlined elastic layer should be noted. Evidence of atherosclerosis or phlebitic changes is not present.

elastic layer which limited it from the surrounding tissue. One of the series of cross sections of the lesser omentum included the right branch of the hepatic artery. Near to it, a large vein was found which showed a narrow lumen caused by a marked thickening of the intima. It consisted of a thick layer of partly hyaline connective tissue with patchy proliferation of elastic fibers. Blood vessels were found within. The media was irregularly compressed, occasionally completely missing. A section including the superior mesenteric artery showed several cross sections of large veins presenting an identical picture, and near the artery there was seen a completely obliterated large vein but no patent blood vessel which would correspond to the superior mesenteric vein. Identical pictures were found in sections from the head of the pancreas and from the hilum of the liver. A section

of the splenic vein showed the narrowed lumen divided by a partition of connective tissue running across the lumen. An intact internal elastic layer was found along the greater part of the circumference. The lesser omentum also contained lymphatic tissue, numerous lymph vessels, nerve trunks and occasional islands of acinar tissue suggestive of pancreas.

Sections of the adenomas with the adjacent liver tissue showed an absence of lobular architecture in the former. They were, however, composed of liver cells, typical in shape and size but of paler cytoplasm than the surrounding parenchyma cells. They even formed cords separated by sinusoids which resembled those of the normal liver tissue. The contact of the cells, however, was not as close as in normal parenchyma and in one of the adenomas a loose arrangement of the cells was conspicuous. It was separated from the surrounding liver tissue by connective

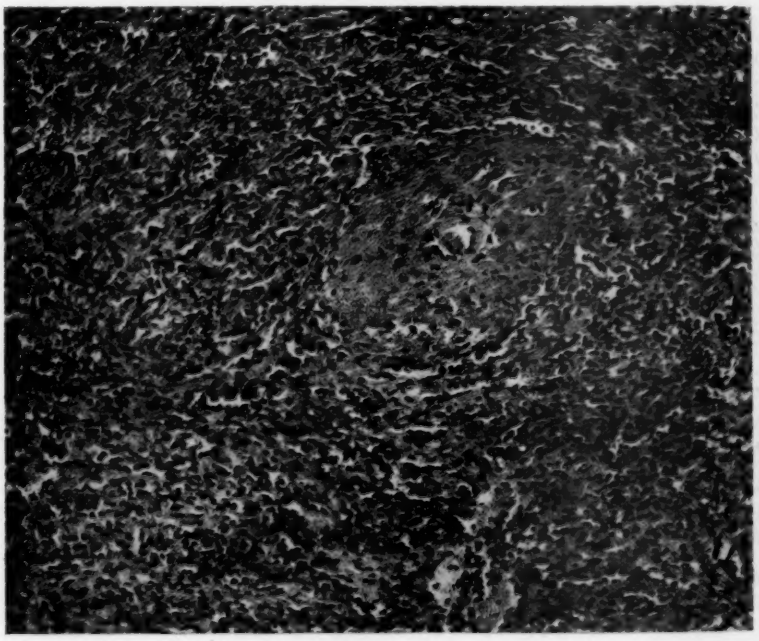

Fig. 5.—Fibrosis of malpighian corpuscles and diffuse fibrosis of the pulp.

tissue whereas the other adenomas for the most part blended with the normal hepatic parenchyma which was only compressed. Interlobular bile ducts were absent, but bile capillaries were demonstrated.

The heart was normal.

Lungs: Edema of the alveoli and an embolus in a large pulmonary artery branch were observed in the lungs.

Changes were not seen in the kidneys.

A section of the suprarenal gland showed a large vein, apparently the main branch of the suprarenal vein, completely filled by a canalized thrombus. The vasa vasorum in the adjacent connective and fat tissue were numerous and conspicuous. The internal elastic layer was found as a distinct wavy band for about half the circumference, and in the other half it showed fragmentation. Many fine elastic fibers were found within the organized thrombus.

Sections from the bone marrow showed a conspicuously large number of megakaryocytes; frequently, pseudopodia-like processes were noticed at their periphery. Numerous structures the size and shape of megakaryocytes were seen without nuclei or with nuclear rests. Numerous erythroblasts, neutrophils, eosinophils, myelocytes and myeloblasts formed the bulk of the marrow. There was still a large cell type which was abundant, with one or two, occasionally rod shaped, nucleoli in a large round sharply limited nucleus and a rim of basophil cytoplasm, which could not be grouped with the myeloblasts. The nucleus resembled the nuclei of megakaryocytes.

The spleen was reexamined. The capsule was normal. The trabeculae were not increased in number and they did not appear to be thicker than normal. However, they were not as sharply outlined from the surrounding pulp as they usually are,

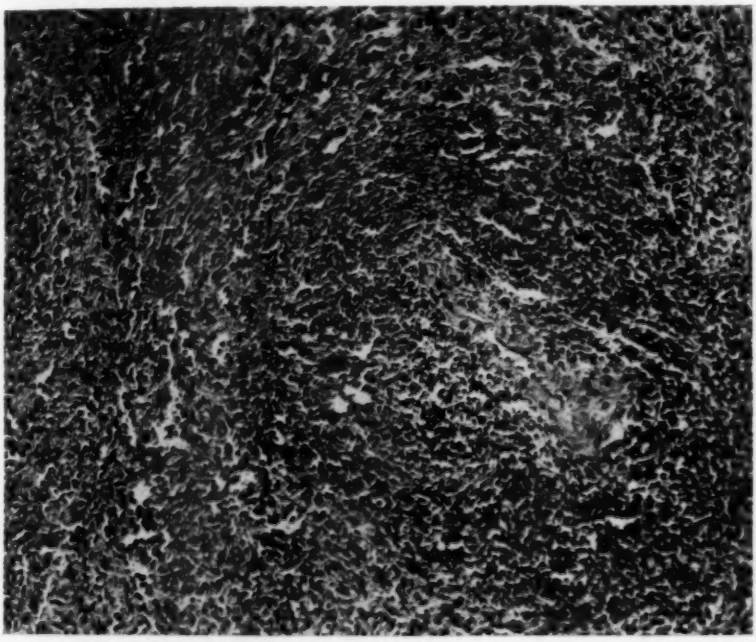

Fig. 6.—Fibrosis around the central artery, with hemorrhage; part of the follicles still intact; sinus hyperplasia.

and connective tissue fibers separated themselves from the edges and blended with the thickened reticulum of the pulp. The lymph follicles were rather scarce and frequently showed fibrosis. There were, however, a fair number of malpighian corpuscles without any change. The lymph follicles showed various degrees of fibrosis. Some were completely transformed into fibrous nodules with the central arteries still visible. For the most part, however, only a portion around the central artery showed a conspicuous thickening of the reticulum fibers combined with a disappearance of the lymphocytes. The reticulum could still be recognized; within its meshes blood was often seen, occasionally so much that the reticulum was obscured. The periarterial thickening of the reticulum extended into the malpighian corpuscles as well as toward the pulp. Not only the intrafollicular but also the prefollicular portions of the arteries showed the same conspicuous change.

TABLE 1.—*Chronologic Review of Reported Cases of*

Author	Sex*	Age Years	Duration of Symptoms	Symptoms	Extent of Cavernous Tissue
Kobrich: Inaug. Diss., Kiel, 1903.....	♂	25	8 yr.	Anemia and splenomegaly for 8 years; hematemesis for 2 years	Last portion of portal vein
Lommel: Arch. f. klin. Med. **87**: 315, 1906	♂	42	3 yr.	Headache; congestion, abdominal pain; final vomitus	At liver hilum and branches; trunk of portal vein recent thrombus
Pick: Virchows Arch. f. path. Anat. **197**: 490, 1909	♀	57	20 yr.	Splenomegaly; terminal gastric hemorrhage	Entire stem
Deve: Normandie méd. **23**: 109, 1908	♀	25	5 yr.	Pain in left side; dyspepsia; hematemesis	Entire stem; cavernomatous formation only within hilum; entire stem thrombosed
Risel: Deutsche med. Wchnschr. **35**: 1685, 1909	♀	34	2 mo.	Hematemesis; terminal peritonitis	Entire stem and hepatic ramification
Loeb: case 2, Inaug. Diss., Bonn, 1909	♂	54	.....	.....	Mesenteric veins and stem; less at hilum
Beitzke: Charité ann. **34**: 466, 1910..	♂	40	7 yr.	Gastric discomfort; occasional icterus; ascites	Entire stem and ramifications
Versé: Ztschr. f. Biol. **48**: 526, 1910..	♂	29	3 yr.	Colic; splenomegaly; terminal severe cramps; hemorrhagic stools; vomiting	Entire stem and intrahepatic branches; splenic vein
Josselin de Jong: Mitt. a. d. grenzgeb. d. Med. u. Chir. **24**: 160, 1911-1912	♀	44	8 yr.	Gastric disturbances; recent icterus	Entire stem and 1.5 cm. intrahepatic branches; entire length 5cm.
Emmerich: Frankfurt Ztschr. f. Path. **10**: 362, 1912	♂	44	6 mo.	Ascites; tumor in left hypochondrium	Entire stem
Hart: Berl. klin. Wchnschr. **50**: 2231, 1913	♀	20	Acute	Hematemesis	Entire stem except for 1 cm. distal
Gruber: case 1, Deutsches Arch. f. klin. Med. **122**: 319, 1917	♂	45	8 mo.	Umbilical pain	Stem and intrahepatic branches
Gruber: case 2, Deutsches Arch. f. klin. Med. **122**: 319, 1917	♀	57	8 to 10 yr.	Symptoms considered as gallstone colic with jaundice; recent loss of flesh; blood in stools; cecal tumor	Stem and 1 cm. intrahepatic branches
Gruber: case 4, Deutches Arch. f. klin. Med. **122**: 319, 1917	♂	28	27 yr.	Hematemesis; ascites; anemia	Terminal portion and intrahepatic branches
Kaspar: case 2, Deutches Ztschr. f. Chir. **156**: 1, 1920	♂	60	7 yr.	Hematemesis; melena; ascites of short duration	From the hilum down to the head of the pancreas
Meyer: Med. Klin. **16**: 876, 1920.....	♀	38	8 yr.	Gastric disturbance; pain; loss of appetite; recent abdominal pains and bilious vomitus	Entire stem and splenic vein

* In this column, ♂ indicates male; ♀, female.

Histology	Liver	Spleen	Collateral Circulation	Cause of Death Remarks
Thrombotic occlusion of portal vein; rupture of elastic layers	Somewhat smaller	12 by 12 by 4 cm.; very tough; increased connective tissue	Esophageal veins	Hemorrhage from ruptured esophageal varix; trauma; presentation by Heller
Portal vein recognizable	Somewhat larger	109 by 122 mm.	Veins of lesser omentum dilated	Acute thrombosis of mesenteric and splenic veins; hemorrhagic infarction of small intestine; polycythemia
Portal vein not recognizable	22 by 22 by 13 cm.	Weight, 1,600 Gm.	Veins of lesser omentum and esophagus	Gastric hemorrhage; sepsis
Portal vein recognizable	Spiegel's lobe enlarged	Weight, 930 Gm.	.....	Thrombosis of splenic, gastric and mesenteric veins
Result of organization of previous parietal thrombi; portal vein recognizable	Weight, 950 Gm.; adenomas	Weight, 750 Gm.; extreme chronic passive congestion	Esophageal veins	Thrombosis of mesenteric veins; gangrene of intestine; scarlet fever at age of 8 years; sick for some time, apparently with ascites
Organized thrombosis of portal vein; the cavernous tissue formed by dilated veins of lesser omentum; portal vein recognizable	Normal	31 by 12 by 5.6 cm.; firm	.....	Tuberculosis of lungs; accidental observation
Malformation; no trace of portal vein	25 by 15 by 7 cm.	Enlarged	Caput medusae	Thrombosis of mesenteric vein and infarction of small intestine; hepatic artery pencil thick
Remnants of portal branches recognizable	Normal	26.5 by 22 by 8 cm.	Esophageal vein, left suprarenal vein	Hemorrhagic infarction of ileum; superior mesenteric vein thrombosis; polycythemia
.....	Weight, 1,600 Gm.	Weight, 1,200 Gm.; sclerosis of pulpic reticulum; sinuses dilated; follicles atrophic	Sappey's veins; esophageal veins; suspensor ligament of liver and teres	Thrombosis of mesenteric vein; hemorrhagic infarction of intestine
Inflammatory changes of the venous wall and the surrounding tissue	Weight, 1,650 Gm.; wide hepatic artery	Weight, 2,000 Gm.; thrombosis of splenic vein	Omental veins	Peritonitis; cachexia; active hematopoietic bone marrow in long bones; possible polycythemia
No trace of venous wall with elastic stain; malformation	Deformed multiple gummas	Much enlarged, fleshy; pulp spaces narrow; follicles small	Esophageal veins	Rupture of a varix; hemorrhage
Small cellular panphlebitis	Weight, 1,550 Gm.	21 by 14 by 6 cm.; congestion of spleen; occasional thrombi	Esophageal veins	Hemorrhagic infaret of intestines; two attacks of appendicitis 5 years before
Syphilitic phlebitis and periphlebitis; mesophlebitis; destruction of elastic layer; obliteration of small veins	Weight, 1,200 Gm.	22 by 9 by 6 cm.; diffuse connective tissue increased	Esophageal veins	Hemorrhagic infaret of intestines; thrombosis of mesenteric and splenic veins
Portal vein recognizable; inflammatory reaction	Weight, 1,510 Gm.	28 by 22 by 9 cm.	Esophageal veins	Rupture of a varix esophagi; thrombosis of mesenteric veins
The elastic layer of the portal vein in places still recognized	Slightly smaller than normal	Enlarged, firm, thrombosis of splenic vein	.....	Hemorrhage from duodenal ulcer
No trace of portal vein	Adenomas	28 by 15 by 8 cm.; fleshy	Gastro-esophageal diaphragmatic right renal veins	Thrombosis of mesenteric vein, gangrene of intestine

TABLE 1.—*Chronologic Review of Reported Cases of*

Author	Sex*	Age Years	Duration of Symptoms	Symptoms	Extent of Cavernous Tissue
Eppinger: Die hepatolienalen Erkrankungen (case 32), Berlin, Julius Springer, 1920	♀	47	7 yr.	Icterus; gallbladder pains; recent sensation of great hunger and thirst; ascites extreme emaciation	Ramification of portal vein
Hulk: Nederl. Tijdschr. v. Geneesk. **67**: 4, 1923	♂	36	3 yr.	Mild abdominal pain; bleeding from gums; some recent bilious vomitus; terminal severe cramps in right side	Stem and intrahepatic ramifications; portal vein above hepatic artery
Kuhr: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **37**: 177, 1924	♂	42	7 yr.	Gastric discomfort; blood in stool; hematemesis; terminal ascites	Terminal portion of portal vein
Gruber: Centralbl. f. allg. Pathol. u. path. Anat. **33**: 205, 1922-1923. Kratzeisen: Virchows Arch. f. path. Anat. **244**: 467, 1923	♂	38	7 yr.	Pains in left hypochondrium; splenomegaly	Only first ramification
Wohlwill: Virchows Arch f. path. Anat. **254**: 243, 1925	♂	59	27 yr.?	General weakness and dizziness; rectal hemorrhage	Hilum
Cabred: Semana méd. **33**: 109, 1926	♂	63	.....	.....	Entire stem and several centimeters of the intrahepatic ramifications
Klemperer and Rosenthal.....	♀	42	9 yr.	First, splenomegaly, anemia and slight ascites; later, gastric hemorrhages and ascites	Entire stem; 1 cm. of intrahepatic ramifications

* In this column, ♂ indicates male; ♀, female.

In this way, many fibrous nodules resembling fibrous splenic corpuscles were seen, which on close examination were not related to the central, but to the prefollicular, artery. The pulp showed, instead of a fine reticulum network, a frame work of thick, fibrous, hyaline fibers, within which the sinuses stood out conspicuously because of the prominent endothelial cells. The lumen was often empty. Occasionally, however, it contained a few red blood cells, eosinophils, leukocytes, lymphocytes and large mononuclear cells. Here and there a cross section of a sinus was almost entirely filled by multinuclear giant cells attached to the wall. Rarely the sinuses were distended and formed small cystlike empty spaces. The splenic cords were formed by the thickened reticulum and contained, aside from the reticulum cells, no other cellular elements. A section from the hilum of the spleen (fig. 6) showed large branches of the splenic artery and a large vein, the lumen of which was markedly narrowed. On elastic stain the internal elastic layer was recognized as a distinct fine wavy line. The lumen was filled to a great degree with a dense hyaline connective tissue.

COMMENT

My case, therefore, was that of a woman, aged 42, in whom a diagnosis of Banti's disease had been made seven years prior to her death, and in whom splenectomy had been performed. The postoperative course was stormy owing to several attacks of thrombosis. After a short period of relative comfort she began to suffer from ascites and gastric hemorrhage which were relieved for short periods by medical treatment. She was readmitted to the hospital on account of ascites,

Cavernomatous Transformation of the Portal Vein—Continued

Histology	Liver	Spleen	Collateral Circulation	Cause of Death Remarks
.....	Small	Three times enlarged	.....	Peritonitis (repeated paracentesis); glycosuria; gallbladder shrunken
No trace of portal vein	Small adenomas	Weight, 600 Gm.	Esophageal veins	Thrombosis of mesenteric vein; gangrene of small intestine; left branch of portal vein not found
Remnants of venous wall recognizable	25 by 18 by 18 cm.	24 by 14 by 7 cm.	Esophageal veins	Anemia and cachexia; rupture of varices of esophagus
No disease, no remnants of endophlebitis	.....	Weight, 1,500 Gm.; thrombosis of veins, cavernous tissue around	.....	Thrombosis of mesenteric vessels; intestinal infarction; polycythemia; thrombi of aorta
Complete calcification	Small	Normal	Few collateral vessels between omentum and liver capsule; hemorrhoidal veins	Infarction of small intestine; alcoholic, portal sclerosis; operation 32 years before for a worm in choledochus
No traces of the portal vein	Small, right lobe atrophic	Three times as large as normal	Esophageal veins	Admitted moribund; no history
Portal vein recognizable throughout	Left lobe atrophic; Weight, 1,500 Gm.; multiple adenomas; wide hepatic artery	Enlarged typical Banti spleen histologically	Esophageal veins; left suprarenal vein; omental veins	Pulmonary embolism; thrombocythemia

severe anemia and increasing weakness due to repeated hemorrhages. When given a blood transfusion the patient suddenly collapsed and died. A remarkable feature of the laboratory evidence was the excessive increase in the number of blood platelets which was first observed after the splenectomy. Autopsy revealed a chronic thrombotic occlusion of the portal vein and its tributaries as well as of branches of the renal and suprarenal veins, and the development of a cavernomatous tissue within the lesser omentum. Death was due to embolism.

The first similar observation was published in 1903 by R. Köbrich.[4] Since then twenty-two new cases have been fully recorded in the world literature, the great majority of reports being in German. A chronologic review of the reports is given in table 1. The age and sex incidence of the patients is tabulated in table 2.

In the majority of cases, death was due either to thrombosis of the superior mesenteric vein, with subsequent hemorrhagic infarction and necrosis of the intestine (eleven cases), or to hemorrhage from the dilated esophageal veins (eight cases). In two cases (Emmerich [5] and

4. Köbrich, R.: Ein Fall von cavernöser Umwandlung der Pfortader, Inaug. Diss., Kiel, 1903.

5. Emmerich, E.: Die Kavernöse Umwandlung der Pfortader, Frankfurt. Ztschr. f. Path. **10**:362, 1912.

Eppinger [6]), peritonitis due to the infection of the ascitic fluid was the cause of death. One case (Loeb [7]) was accidentally discovered at the autopsy of a patient dying of pulmonary tuberculosis. In my case, death was due to embolism of the pulmonary artery. The duration of the disease varies from two months (Risel [8]) to twenty-seven years (Gruber,[9] case 4; Wohlwill [10]), the vast majority of cases lasting from three to nine years. In the consideration of the clinical symptoms one has to distinguish between the acute, terminal and the chronic symptoms. In the patients who died from intestinal infarction, colicky pains and vomit-

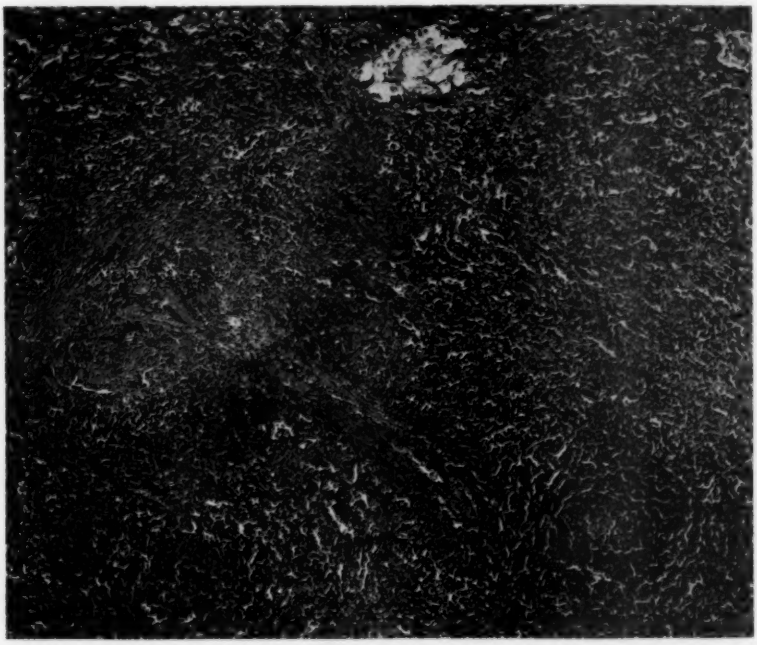

Fig. 7.—Two normal malpighian corpuscles; fibrosis around the prefollicular portion of a central artery; sinus hyperplasia and sinus cysts.

6. Eppinger, H.: Die hepatolienalen Erkrankungen, Berlin, Julius Springer, 1920.

7. Loeb, J.: Ueber zwei bemerkenswerte Fälle von Pfortaderthrombose, Inaug. Diss., Bonn, 1909.

8. Risel, W.: Ein Beitrag zur thrombotischen Obliteration und kavernösen Umwandlung der Pfortader, Deutsche med. Wchnschr. **35**:1685, 1909.

9. Gruber, G. B.: Beiträge zur Pathologie der daueernden Pfortader-Verstopfung, Deutsches Arch. f. klin. Med. **122**:319, 1917.

10. Wohlwill, F.: Ueber Pfortadersklerose und Banti ähnliche Erkrankungen, Virchows Arch. f. path. Anat. **254**:243, 1925.

ing were the most common symptoms pointing to an acute abdominal disease. Severe gastric hemorrhage causing acute anemia was reported in the other main group. In these instances the terminal hemorrhage was mostly preceded by repeated hemorrhages extending over a period of many months or even years. In the other group of cases the history of the patients showed epigastric pains for a considerable length of time prior to death. In one case (Versé [11]) there were colicky abdominal pains three years before death, like those which preceded death. Occasionally (Risel,[8] Gruber,[9] case 4), repeated hemorrhages occur prior to death, owing to intestinal infarctions. Jaundice was reported four times; ascites occurred in six instances. Five times only, splenic enlargement, or symptoms suggesting it, was noticed during life. But one may already anticipate that it was found in all but one instance at autopsy.

In regard to the extent of the replacement of the portal vein, the entire trunk and the first intrahepatic ramifications were generally involved. In some instances, however, there was replacement by

TABLE 2.—*Age and Sex Incidence*

Age	Female	Male	Together
10 to 20	1	..	1
20 to 30	1	3	4
30 to 40	2	3	5
40 to 50	3	4	7
50 to 60	3	2	5
60 to 70	..	1	1
Total	10	13	23

cavernous tissue only in the terminal portions of the main stem, but the intrahepatic branches were more widely involved. In a few instances (Beitzke,[12] Josselin de Jong [13]), the entire vein and the intrahepatic branches were involved. The portal vein could still be recognized, either grossly or microscopically, in thirteen cases. In three cases, the report was not clear on this point; in six cases no trace of the vein was found. The liver was normal in size or even larger in eleven cases. Eight times it was smaller than normal; twice there was not any record of this point. In one case it was altered in size and shape by the presence of multiple gummas. In three cases multiple adenomas were found.

The occurrence of multiple adenomas of the liver in three cases of twenty-two deserves brief consideration. Risel explained them as regenerative hyperplastic nodes following focal necrosis. The necrosis either

11. Versé, M.: Ueber die cavernöse Umwandlung des periportalen Gewebes bei alter Pfortaderthrombose, Beitr. z. path. Anat. u. z. allg. Pathol. **48**:526, 1910.

12. Beitzke, H.: Ueber einen Fall von Kavernöser Umwandlung der Pfortader, Charité ann. **34**:466, 1910.

13. Josselin de Jong, R.: Ueber die Folgen der Thrombose im Gebiete des Pfortadersystems, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:160, 1911-1912.

could have occurred during the scarlet fever in childhood or could have been the result of small infarctions due to occlusion of minute portal branches. Meyer believed in malformation (Keimausschaltung), whereas Hulk was inclined to consider them as a coincidental observation. I rather follow Risel's explanation and consider the adenomas as regenerative formations, especially because in my case other evidence of structural damage was found in the atrophy of the left liver lobe.

In the majority of cases there was a well developed collateral circulation, the connection between portal and general circulation via vena coronaria, esophageal veins, vena azygos, vena cava inferior being the most important collateral route. However, mention has also been made of other collaterals, such as Sappey's veins (Josselin de Jong [13]), caput medusae (Beitzke [12]) and branches of the right renal vein (Meyer [14]). The presence of the cavernous tissue around the splenic vein was reported but once and there was no record of the simultaneous occurrence of cavernous tissue elsewhere. The hepatic artery was mentioned as being wide and thickened in three cases; in one instance (Hulk [15]) it was found behind the portal vein.

The macroscopic appearance in all the observations was fairly identical; the interpretation of the pathogenesis, however, varied. Whereas the majority of the writers considered the cavernous tissue within and around the portal vein as the result of a recanalization of a portal thrombosis, Pick,[16] Beitzke,[12] Hart,[17] Meyer [14] and Cabred [18] differed in their respective interpretations. The absence of any evidence of even remnants of the portal vein on microscopic examination in their cases spoke, they believed, against the explanation given by the other authors. Pick's conception of the cavernous transformation was that of a hemangioma of the portal vein. Beitzke and Hart believed that the absence of the portal vein due to malformation accounted for the cavernous tissue within the lesser omentum, whereas Meyer and Cabred combined both theories and explained the cavernous formation in their observations as an angiomatous tumor on the base of a malformation. It is true that the lack of any trace of a portal vein militates against an old canalized portal thrombus, because the elastic fibers would remain as evidence even years

14. Meyer, F. G.: Ueber die kavernöse Umwandlung der Pfortader, Med. Klin. **16**:876, 1920.

15. Hulk, J. F.: Over caverneuse omvorming rondom de Portader, Nederl. Tijdschr. v. Geneesk. **67**:4, 1923.

16. Pick, L.: Ueber totale hämangiomatöse Obliteration des Pfortaderstammes und über hepatopetale Kollateralbahnen, Virchows Arch. f. path. Anat. **197**:490, 1909.

17. Hart, C.: Ueber die cavernöse Umwandlung der Pfortader, Berl. klin. Wchnschr. **50**:2231, 1913.

18. Cabred, R. G.: Consideraciones sobre un raro tumor angiocavernomatoso del tronco porta, Semana méd. **33**:109, 1926.

after complete closure of the lumen. It is difficult to disregard the validity of such a histologic argument, and one has to accept the contention of the foregoing writers that the cavernous tissue in place of the portal vein is not always the result of thrombus canalization. However, I cannot follow Beitzke's and Benda's argumentation that the presence of nerve trunks between the veins of the cavernous tissue speaks against thrombus organization. In the case here reported there could not be any doubt as to the pathogenesis, because the portal vein, occluded by a canalized thrombus, was found in every section. Nevertheless, small nerve trunks were present between the vascular spaces which constituted the cavernous tissue. This fact is not surprising if one considers that the spongy vascular tissue in my case as well as in other cases was not limited to the original lumen of the portal vein, but is located within the entire hepatoduodenal ligament. It is not the recanalization of the thrombus alone but far more the opening of collateral veins within the wall of the portal vein, namely, its vasa vasorum, and blood vessels within the lesser omentum, which gives rise to the formation of a cavernous tissue within and around the portal vein. The presence of nerve trunks, lymph glands and vessels, or an occasional small island of pancreatic tissue, in the lesser omentum is a normal occurrence, and one can understand that such structures are found between the veins of the cavernous tissue.

The conception here presented that the formation of cavernous tissue is the result of not only canalization of a portal thrombosis but far more of the opening of collaterals within the lesser omentum accounts for the extent of the spongy vascular tissue in my case as well as in other cases. Here one may speculate whether a primary early phlebitis of the portal vein, with subsequent thrombosis at the root of the whole process, could not account for the complete destruction of the venous wall in other cases. It is possible then that an inflammation of the venous wall would extend into the surrounding lesser omentum. The question may be asked whether, in the further course of such events, the dilatation of newly formed capillaries and veins could not produce a picture suggestive of a vascular tumor. Whatever the course may be, however, the cases thus far reported can be classified into three groups, according to the explanation of the cavernomatous transformation: (1) end-result of portal thrombosis; (2) malformation, and (3) tumor (angioma of portal vein).

My case is in accord with the reports in the literature. The duration of the condition was at least nine years; the main symptoms were such that a diagnosis of Banti's disease was made and a splenectomy was performed. The question must be raised whether the portal occlusion was not the result of the operation. The histologic picture and diagnosis at the time of operation was merely that of Banti's fibro-adenia. How-

ever, I was able to reexamine a part of the original specimen and was fortunate enough to find evidence in one section of an old completely organized and recanalized thrombosis of the splenic vein (fig. 6).

Since the existence of an old thrombosis of the splenic vein at the time of the splenectomy militates against the operation as its causative factor one must look for another etiologic explanation of the cavernomatous transformation of the portal vein in this case. The presence of an organized and canalized thrombus of the portal vein places this case in the first of the three groups mentioned. Since the cavernomatous tissue in this group of cases is the result of dilatation of vasa vasorum and capillaries consequent on a thrombotic occlusion of the portal vein, the cause of its formation is coincident with that of the chronic portal thrombosis in general.

Chronic thrombosis of the portal vein or thrombophlebitis adhesiva (Rokitansky,[19] Frerichs [20]) can be the result of a multitude of causes. These cases can be classified according to the principles accepted for the causes of thrombosis in large veins in general, into the following groups:

1. Compression of the venous wall (neoplasms, tuberculous lymph glands, gummas in the hilum of the liver, gallstones, old inflammatory scars in the vicinity or duodenal ulcers [Kaspar,[21] Frerichs [20]], peritoneal bands [Brahme [22]] and malformation [Gruber,[23] Hulk [15]]).
2. Retardation of the portal circulation:
   (*a*) General causes.
   (*b*) Local causes (cirrhosis and syphilis of the liver [Pfifferling,[24] Klemm [25]]).
3. Disease of the venous wall:
   (*a*) Nonsyphilitic inflammation.
   (*b*) Syphilitic inflammation.
   (*c*) Trauma.
   (*d*) Primary sclerosis.
4. Changes in the composition of the blood:
   (*a*) Polycythemia.

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19. Rokitansky, K.: Lehrbuch der pathologischen Anatomie, Vienna, Braumüller & Sohn, 1863.

20. Frerichs, T.: Krankheiten der Pfortader II Braunschweig, F. Vieweg & Sohn, 1861.

21. Kaspar, F.: Beiträge zur Kenntnis des Verschlusses im Pfortader-stamm, etc., Deutsche Ztschr. f. Chir. **156**:1, 1920.

22. Brahme, L.: Ein Fall von chronischem Portahinderni:, Acta med. Scandinav. **61**:175, 1924-1925.

23. Gruber, G. B.: Zur Kasuistik der Pfortaderthrombose, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:734, 1913.

24. Pfifferling, S.: Ueber einen Fall von Lebersyphilis mit Pfortaderthrombose und Darmhaemorrhagien, Inaug. Diss., Munich, 1902.

25. Klemm, E.: Pfortaderthrombose bei Lebersyphilis mit tödlicher Magen-und Darmblutung, Inaug. Diss., Munich, 1903.

Concerning classification 3, a certain group of cases of portal thrombosis, acute as well as chronic, is apparently coincident with the puerperium (Rommelaere,[26] Bucura,[27] Linzenmeier [28]). Since the present conception of thrombosis during the puerperium is that it is inflammatory in origin, these cases can, for the present, be placed in the third group. Owing to the intimate relationship which exists between purulent thrombophlebitis of the portal vein and suppuration within the organs draining into the vein, a number of authors have suggested that a milder form of inflammation could be responsible for chronic thrombophlebitis of the portal vein. Gohrbandt [29] and Gruber [9] (case 1) have reported cases of chronic nonpurulent portal thrombosis following appendicitis. It is self-evident that chronic inflammation in the vicinity of the portal vein, such as cholecystitis and gastric and duodenal ulcers, may cause thrombosis not only by compression of the lumen but also by extension of the inflammation to the wall.

The origin of chronic thrombosis of the portal vein in traumatism to the vessel was first proposed by Heller [30] who is also responsible for the reports of Köbrich,[4] Wilke [31] and Edens.[32] Ponfick,[33] Saxer [34] and Schmorl [35] at the same time reported similar observations. The picture and the description of Heller's case show irregular interruption in the internal elastic layer as well as ruptures in the media. These are partly filled with homogeneous thrombi, and partly with leukocytes. Although the histologic evidence could be construed as some proof for the assumed etiology, the clinical history in this and other cases is not convincing. In Heller's first case as well as in other cases the trauma was slight. In Köbrich's and in Edens' case definite trauma could not be ascertained, but it was assumed that some trauma must have occurred.

26. Rommelaere, M.: La pylethrombose, Bull. Acad. roy. de méd. de Belgique **19**:79, 1905.

27. Bucura: Mesenterialgefässverschluss nebst einem Beitrag zur allgemeinen Thrombosenätiologie, Arch. f. Gynäk. **119**:275, 1923.

28. Linzenmeier: Ein Fall von Pfortaderthrombose im Wochenbett, Monatschr. z. Geburtsh. u. Gynäk. **67**:59, 1924.

29. Gohrbandt, E.: Pfortadersklerose als Folgeerscheinung von Appendicitis, Berl. klin. Wchnschr. **57**:977, 1920.

30. Heller, A.: Ueber traumatische Pfortaderthrombose, Verhandl. d. deutsch. path. Gesellsch. **7**:182, 1904.

31. Wilke, A.: Pfortaderthrombose und Trauma, Inaug. Diss., Kiel, 1903.

32. Edens: Ueber Milzvenenthrombose, Pfortaderthrombose und Bantische Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:59, 1908.

33. Ponfick: Verhandl. d. deutsch. path. Gesellsch. **5**:133, 1902.

34. Saxer, F.: Verhandl. d. deutsch. path. Gesellsch. **5**:133, 1902; Beiträge zur Pathologie des Pfortaderkreislaufs, Centralbl. f. allg. Path. u. path. Anat. **13**:577, 1902.

35. Schmorl, in discussion of Ponfick (footnote 33).

The reasoning of the authors to prove their point is not convincing, and one is not surprised to find that the traumatic etiology of portal thrombosis was subsequently fully neglected.

Of far greater importance is the question of portal sclerosis and portal thrombosis. Borrman,[36] in 1897, first reported on primary sclerosis of the portal vein, which he compared with arteriosclerosis. He collected several cases from the literature and added observations of his own. Borrman's standpoint was strongly opposed by Saxer,[34] who believed that the sclerosis found in cases of portal thrombosis is the result and not the cause of the organization of the thrombus. Buday,[37] however, in 1902, and especially Simmonds,[38] in 1912, not only upheld Borrman's point of view, but was able to add important new facts in favor of the primary portal sclerosis, independent of thrombosis or increased pressure in the portal system as in cirrhosis of the liver. Whereas, Borrman,[36] Buday [37] and Simmonds [38] believed that syphilis is one of the main causes of portal sclerosis, Winkler,[39] in 1915, attempted to introduce a constitutional factor into the etiology of this disease. He found in one case an atrophy of the muscular wall of the vein and questioned whether a congenital weakness of the musculature of the portal vein could not be responsible for the proliferation of the intima.

Concerning classification 4, alteration in the composition of the blood combined with portal thrombosis was first reported by Lommel,[40] who observed a case of polycythemia with splenomegaly. At autopsy a cavernomatous tissue was found in place of the portal vein. Death was due to an acute thrombosis of the portal vein and its tributaries. Whereas Lommel favored the idea of the polycythemia being the result of the portal occlusion, Brie,[41] Gruber,[42] Kratzeisen,[43] Sauer [44] and

36. Borrman, K.: Beiträge zur Thrombose des Pfortaderstanumes, Deutsches Arch. f. klin. Med. **59**:283, 1897.

37. Buday, K.: Ueber die Sklerose der Pfortader, Centralbl. f. allg. Path. u. path. Anat. **14**:160, 1903.

38. Simmonds, M.: Ueber Pfortadersklerose, Virchows Arch. f. path. Anat. **207**:360, 1912.

39. Winkler, H.: Ueber primäre Pfortaderthrombose bei Pfortader-sklerose und bei chronischem Milztumor, Frankfurt. Ztschr. f. Path. **17**:377, 1915.

40. Lommel, F.: Ueber Polycythemie mit Milztumor, Deutsches Arch. f. klin. Med. **87**:315, 1906.

41. Brie, F.: Ueber die Thrombose der Pfortader, Inaug. Diss., Leipzig, 1914.

42. Gruber, G. B.: Polycythämie und Pfortaderthrombose, Centralbl. f. allg. Path. u. path. Anat. **33**:205, 1922-1923.

43. Kratzeisen, E.: Polycythämie und Pfortaderthrombose, Virchows Arch. f. path. Anat. **244**:467, 1923.

44. Sauer, G.: Milzestirpation bei Polyzythaemia rubra (morbus Vaquez), Deutsche. med. Wchnschr. **50**:1641, 1924.

Brandenberg [45] considered the polycythemia as the cause of the thrombotic occlusion of the portal vein in their cases. Polycythemia was also present in the cases of Versé [11] and Emmerich.[5]

If an attempt is made to trace the origin of the portal thrombosis in my case evidence is not found of any of the points enumerated in groups 1, 2 or 3. Here particular attention may be called to the fact that the wall of the portal vein did not show any alteration or any evidence of inflammation, traumatism or atherosclerosis. Therefore, one reaches by exclusion, group 4—that is, alteration in the composition of the blood—as the probable cause of the thrombosis in my case. Is there any positive proof in the observed facts to support such a conclusion? The objection that the portal thrombosis could have been the result of the splenectomy could be dismissed because of the observation of an old occlusion of the splenic vein existing already at the time of operation. But the exact date of the first occurrence of the thrombosis within the portal system could not be ascertained. However, clinical and pathologic observations made during the further course threw light on the pathogenesis. Soon after the splenectomy was performed, symptoms prevailed which pointed to a thrombosis of the mesenteric vein. Within the next week thrombosis of the jugular and saphenous veins occurred. At autopsy thrombotic occlusion of the suprarenal and left renal veins besides those of the portal system was found. The multiplicity of the thromboses, as well as the absence of any structural changes within the wall of the veins involved, necessitates the conclusion that only changes in the coagulability of the blood could have been responsible for the repeated and widespread thrombus formation. The existence of such a condition, however, is not a speculation but is proved by the observation of a highly increased number of blood platelets during life.

The first observation of the enormous increase of the thrombocytes in this case, to a height of 1,500,000 per millimeter, was made by Dr. Rosenthal immediately after splenectomy. Repeated examination showed similar values. Furthermore, it was noted that the formation of thrombi within the saphenous and jugular veins, as recognized clinically, was preceded by a sharp drop in the platelet count. The figures rose again, only gradually reaching, after a month, the unusually high level. Rosenthal concluded that in the process of thrombus formation an enormous number of platelets must have been removed from the circulating blood, which accounted for the rapid decrease. That there is an increase in the number of blood platelets after hemorrhage and after

45. Brandenberg, R.: Ueber das Verhältnis zwischen Polycythaemia und Pfortaderthrombose, Acta path. et. microbiol. Scandinav. **3**:521, 1926.

splenectomy is well known (Ogata,[46] Brill and Rosenthal[47]), but under such conditions the increase is only transient, and after a relatively short time they return to their previous values. In the case here reported, however, the extreme figures of over 1,000,000 were found for a period of seven years. Permanent increase in the number of platelets has been reported by Minot and Buckman[48] in cases of chronic myelogenous leukemia. N. Rosenthal[3] was the first to call attention to a thrombocythemic form of Banti's disease and the case here reported was one of his series. He reported three more cases showing excessive figures of thrombocytes, in which also there were repeated thromboses. Rosenthal considered the high platelet count the result of the splenectomy, but he referred to other cases he had observed in which similar blood platelet crises occurred without operation. From the evidence of thrombotic occlusion of the splenic vein at the time of operation the conclusion must be reached that in this case also the thrombocythemia preceded the splenectomy. Thrombophlebitic splenomegaly and a high platelet count were reported only casually by Kaznelson[49] in two cases. He referred to the obscure pathogenesis of these cases and warned against splenectomy. In his cases, too, there was thrombosis of other veins.

The conception of Wright[50] as to the origin of the blood platelets from the megakaryocytes has become almost universally accepted. It seems interesting to note, therefore, that the number of megakaryocytes in my case was conspicuously increased over the normal. One is tempted to consider this feature as an evidence of a primary hyperplasia of the bone marrow giant cells which would account for the constitutional thrombocythemia. I shall refrain from attributing too much significance to this observation, however, because of the anemia of the patient, since an increase in the megakaryocytes was observed by Ogata[46] in experimental anemia in rabbits. According to the observations of H. Frey,[51] he found an excessive number of megakaryocytes in polycythemia. It may be well to recall that polycythemia as a cause of portal thrombosis

46. Ogata: Unters über die Herkunft der Blutplättchen, Beitr. z. path. Anat. u. z. allg. Pathol. **52**:192, 1911.

47. Brill, N. E., and Rosenthal, N.: The Curative Treatment by Splenectomy of Chronic Thrombocytopenic Purpura Hemorrhagica, Am. J. M. Sc. **166**:503, 1923.

48. Minot, G. R., and Buckman, T. E.: The Blood Platelets in the Leukemias, Am. J. M. Sc. **169**:477, 1925.

49. Kaznelson, P.: Erfahrungen über die Indikationen der Splenektomie und über deren Wirkungsmechanismus, Wien. Arch. f. inn. Med. **7**:87, 1923.

50. Wright, H. H.: Die Entstehung der Blutplätchen, Virchows Arch. f. path. Anat. **186**:55, 1906.

51. Frey, H., in Askanazy, H.: Handbuch der speziellen pathologische Anatomie und Histologie, Berlin, Julius Springer, 1927.

is well represented in the quotations from the literature. From the clinical and anatomic evidence one cannot fail to reach the conclusion that the original portal thrombosis in the case here reported was caused by an altered composition of the blood, most probably a thrombocythemia.

It is of interest, finally, to correlate the clinical picture with the anatomic observations. At the time of her first admission the patient presented a syndrome (splenomegaly, anemia and low leukocytic count without any apparent cause) highly suggestive of Banti's disease. The microscopic picture of the spleen corroborated the clinical diagnosis, since the histologic features considered by Banti [52] as characteristic were present. Even the criteria laid down by Dürr [53] as addenda to the original description were not missing, such as sinus hyperplasia and and "Trabeckel Aufsplitterung." However, the portal thrombosis was certainly present at that time, and was not the result of the operation or of a postoperative thrombosis. The reason for such a contention can be found in two facts: (1) in the presence of a slight ascites at the time of the patient's first admission (table 1), and (2) in the presence of an organized thrombosis of the splenic vein at the time of the splenectomy. This point calls for more detailed consideration. Endophlebitis of the splenic vein is one of the criteria of the Banti spleen, and one could object that the thrombosis of the splenic and portal vein in my case was the result of such an endophlebitis, as the spleen so fully conforms with the Banti spleen. Banti spoke of sclerotic endophlebitis and described the intima as being irregularly thickened and composed of hyaline fibrous bundles with occasional atheromatous or calcified foci. This, together with degenerative processes and ruptures of the elastic lamellae of the media, are the features of portal sclerosis as described by Simmonds. Phlebosclerosis of inflammatory origin must show, according to Benda, proliferation of the connective tissue within the media and the adventitia. None of these features was found in the splenic or portal vein in the case here reported. On the contrary, the outstanding detail which can be recognized in the histologic preparations is the sharp limitation of the internal elastic layer and the unaltered condition of the media and adventitia. The histologic evidence, therefore, rules out an interpretation of the thrombosis of the splenic and portal veins as a result of a primary endophlebitis. It is only logical, then, to conclude that the splenomegaly with the morphologic picture apparently typical of Banti's disease was the result of the previous thrombosis in the portal system.

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52. Banti, G.: Ueber morbus Banti, Folia haemat. **10**:33, 1910; Splenomegalie mit Lebercirrhose, Beitr. z. path. Anat. u. z. allg. Pathol. **24**:21, 1898.

53. Dürr, R.: Bantimilz und hepatolienale Fibrose, Beitr. z. path. Anat. u. z. allg. Pathol. **72**:418, 1894.

That splenomegaly and secondary anemia, the picture of the so-called Banti's disease, is associated with thrombosis of the splenic or portal vein is well illustrated by numerous observations. Rommelaere,[54] in 1903, called attention to the fact that one form of primary splenomegaly is caused by a splenophlebitis or pylethrombosis. Edens,[55] in 1908, reported a case of splenomegaly with anemia and a low leukocyte count which was diagnosed as Banti's disease. The autopsy revealed a portal thrombosis. Cauchois [56] in the same year collected a number of similar cases and added a new observation. He ably emphasized the importance of the syndrome, splenomegaly and anemia of pylethrombotic origin. Cauchois was emphatic in refuting Banti's conception, and strictly warned against splenectomy in such cases. In 1910, Warthin [57] reported several cases and discussed the question of Banti's disease, splenic anemia and portal thrombosis. He concluded that "every factor of the symptom complex that Osler lays down as the criterion for splenic anemia is also a factor in the complex of portal sclerosis and thrombosis." Eppinger [6] devoted a whole chapter in his book to the question of the thrombophlebitic splenomegaly and reported several observations. Further cases were reported by Hart [58] and Wohlwill who stated that portal sclerosis, as well as portal thrombosis, can well produce a clinical picture like Banti's disease. That the histologic criteria of Banti are not specific and that identical pictures occur in cases of portal stasis, such as in cirrhosis of the liver, was shown by Mennet [59] and lately by Dürr.[53] The origin of the Banti picture in my case can still be recognized in the presence of sinus cysts as an evidence of chronic stasis.[60] The case here reported supports, therefore, the previous conclusions about the relationship between portal thrombosis and the picture of Banti's disease.

A new point of view, however, can be found in the correlation of these observations with the important ones of N. Rosenthal. The differentia-

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54. Rommelaere, M.: La pathologie de la veine porte, Bull. Acad. roy. de méd. de Belgique **17**:587, 1903.

55. Edens: Ueber Milzvenenthrombose, Pfortaderthrombose und Bantische Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:59, 1908.

56. Cauchois, H.: Splenomegalie chronique d'origine pylethrombosique, Thèse de Paris, Paris, Steinheil, 1908.

57. Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Vein to Splenic Anemia and Banti's Disease, Internat. Clin. **4**:189, 1910.

58. Hart, C.: Ueber die Bedeutung der Pfortadersklerose, Arch. f. klin. Chir. **118**:337, 1921.

59. Mennet: Die Bantische Krankheit und ihre Beziehumgen zur Lebercirrhose, Virchows Arch. f. path. Anat. **227**:266, 1920.

60. Brief mention should also be made of giant cells within the sinuses because of their occurrence in cases of thrombophlebitic splenomegaly (Bonne, G.: Ein Beitrag zur Kenntnis der Thrombosen der vena lienalis, Inaug. Dis., Göttingen, 1884, Eppinger [footnote 6]).

tion of a thrombocytopenic and a thrombocythemic form of Banti's disease is of the greatest importance, because it allows a selection of cases suitable and unsuitable for operation. Not only is the thrombocythemic group, according to Rosenthal, uninfluenced by splenectomy, but the operation actually endangers the life of the patient. The evidence obtained at necropsy in one of these cases accounted for the failure of the splenectomy. That portal thrombosis is compatible even with comfortable life is evidenced by many observations. Splenectomy in such cases not only is valueless but may cause fatal thrombosis of the mesenteric veins. The recognition of the condition is, therefore, of the utmost importance. While it is not desirable to draw rigid conclusions from one case, it may be suggested here that one should search for evidence of portal thrombosis in all the thrombocythemic cases of Banti's disease. The attention of the clinician should be focused to the relationship between so-called Banti's disease and splenomegaly due to portal thrombosis.

SUMMARY

1. A case of cavernous transformation of the portal vein is reported, and the literature is reviewed.

2. Thrombocythemia is the cause of the portal thrombosis in the case reported.

3. The thrombocythemic form of Banti's disease is possibly caused by chronic portal thrombosis.

MIXED TUMORS OF THE PALATE*

H. E. EGGERS, M.D.
OMAHA

The term "mixed tumor" as applied to neoplasms of complex structure, while unsatisfactory in that it does not give any idea of their derivation, is at present probably the most applicable term; it conveys some idea of their composition and leaves the mode of origin in an obscurity corresponding to that of actual knowledge.

While these tumors are of frequent occurrence in the salivary glands —they constitute the commonest tumor of the parotid—their occurrence elsewhere in the general oral-facial region is much more unusual. As concerns mixed tumors of the palate, they are rather rare, although this is the most frequent site with the exception of the parotid and submaxillary glands. Altogether, in a rather careful survey of the literature, I have been able to collect published accounts of over 100 tumors of this sort. The number is given indefinitely, as it includes some recorded cases in which the microscopic description was lacking or was so inadequate as to leave the diagnosis open to doubt. In addition, a number of cases are not included in this report, as the publications in which the reports appeared—most of them were inaugural dissertations or theses—were inaccessible.

In published accounts with adequate microscopic descriptions which were accessible, eighty-seven tumors were described in such fashion that their morphology could at least be surmised with some probability. Table 1 shows the result of an analysis of these reports as concerns the four tissue elements most frequently observed. Other elements, of less frequent occurrence and not included in the table, are fatty tissue and bone. Five cases are reported here for the first time and are given in the table. The material of case 1 reported here, was referred for diagnosis by Dr. C. G. McMahan of Superior, Neb. Case 2 was furnished by Dr. Joseph Beck of Chicago; cases 3 to 7 inclusive, by Dr. A. C. Broders of the Mayo Clinic. Cases 6 and 7 are adenomas, included here because of their indirect bearing on the subject of the mixed tumors.

REPORT OF CASES

A detailed report on these specimens follows:

CASE 1.—The tumor was almost spherical, only slightly lobulated and about 15 mm. in diameter. It was firm and somewhat elastic, and the cut surface was slightly glistening, uniformly white and did not show distinctly visible surface markings. It had been removed from the soft palate on the right side, where

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it was located about halfway up the vault, anterior to the glossopalatine arc. The patient was a woman, aged 45; the tumor had been present for from fifteen to twenty years without causing trouble, but had apparently grown somewhat during the last six months.

Microscopic examination showed the tumor to be surrounded by a thin capsule of connective tissue, immediately beneath which were a number of parallel clefts, lined with an epithelium which, in its simplest form, was composed of a single layer of cuboidal cells; more usually there was a double layer, while in some places the cells were piled into several layers. Similar clefts ran into the substance of the stroma, and in these, from the epithelial lining of the type described, there could be seen two lines of divergence—into characteristic stratified squamous epithelium, with typical pearl formation on the one hand, to a single layer of

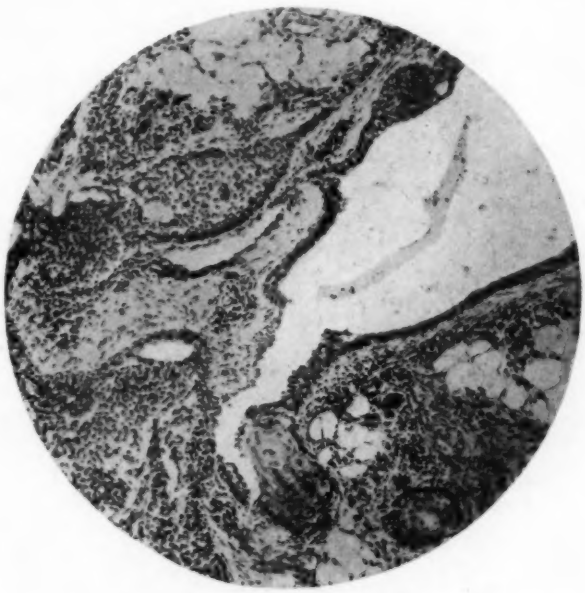

Fig. 1 (case 1).—Squamous and glandular epithelium and mixed stroma.

distinctly columnar epithelial cells on the other. Occasional large cell aggregates, definitely encapsulated, were present, apparently formed by closely packed cells of the cuboidal type. Scattered throughout the tumor were other epithelial structures, usually tubular and frequently with central laminated keratinization, but in some cases without this, and with a wall apparently formed of several layers of cuboidal cells. In some of these the center was occupied by unorganized material readily distinguished from the central keratinization just mentioned. In many areas the epithelium, particularly that of squamous type, appeared to be infiltrating the surrounding stroma in a manner identical with that of malignancy. The stroma was composed in large part of mucoid connective tissue, with frequent hyaline areas suggestive of a cartilaginous matrix. In some sections, a few cartilage cells could be seen in these areas. These hyaline regions, with or without cartilage cells, merged imperceptibly with the typically mucoid tissue. At rather frequent intervals there were groups of fat cells.

The remaining material, which was received in the form of blocks, will be described only from the microscopic point of view.

CASE 2.—As regards contained tissue elements, this was of much simpler composition than case 1. The great bulk of the tumor was formed of a cartilaginous matrix, containing fairly numerous cartilage cells. Enclosed within this were large islands of mucoid connective tissue, and near the centers of these were groups of usually cuboidal epithelial cells, as a rule occurring in indefinite masses, but occasionally showing rudimentary tubule formation. While the individual cells of these masses were sometimes greatly flattened, there was nowhere the slightest evidence of keratinization. There was an apparent merging of the epithelial cells into the mucoid stroma, both in the form of intercellular fibrillae and cellular projections. The mucoid tissue in turn merged imperceptibly with the cartilage.

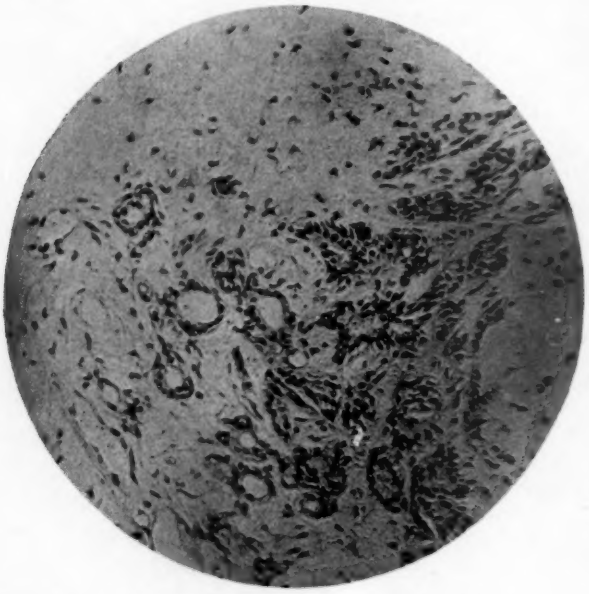

Fig. 2 (case 2).—Apparent blending of epithelium and stroma.

CASE 3.—The tumor was surrounded by a capsule of fibrous connective tissue, from which septums extended into its body, dividing it into lobules. These consisted almost wholly of massed epithelial cells, which occasionally showed a rather definite tubular arrangement. For the most part, however, this was lacking, and the cells were piled together without trace of structural arrangement. The individual cells in the latter case were polygonal unless free from surrounding pressure, when they were circular. Within the masses were cavities lined with flattened cells otherwise the type described and containing precipitated albuminous material. There was usually little stroma within the lobules; when present to any great degree, it took the form of islands of mucoid connective tissue or of fat. In such regions there was no sharp differentiation possible between the mucoid connective tissue and the epithelial cells. The larger septums usually

showed marked hyaline degeneration. Cartilage or squamous epithelium was not found.

CASE 4.—In what was apparently the capsule of the tumor were definitely tubular structures, usually lined with several layers of columnar cells. The bulk of the tumor was formed of dense masses of epithelium, columnar where attached to the connective tissue base, but becoming progressively flattened and laminated as the centers of the masses were approached, and with frequent concentric whorls suggestive of epithelial pearls but without any evidence of keratinization. The stroma took the form of septums, usually delicate, of hyaline connective tissue; where more abundant, it was mucoid, and contained tubules similar to those in the capsule as well as infiltrating cords of apparently glandular cells. In these regions scattered cells, apparently epithelial, merged imperceptibly with the stroma. Cartilage was not observed.

Fig. 3 (case 3).—Apparent blending of epithelium and stroma, and growth of infiltrative type.

CASE 5.—The specimen was formed almost entirely of dense connective tissue, as a rule showing advanced hyaline degeneration, and frequently small areas of calcification. In clefts of this dense stroma were clusters of epithelial cells, some reaching considerable dimensions, all without a trace of structural arrangement. Near these, isolated cells of the same type could often be seen located in small openings of the connective tissue. The epithelial cells were rather small and cuboid. There was little or no apparent blending between these and the connective tissue. This tumor is included among the mixed tumors with some doubt as to its properly coming under this classification.

CASE 6.—This tumor was separated from some mucous glandular tissue which had been removed along with it, by a definite connective tissue capsule, from

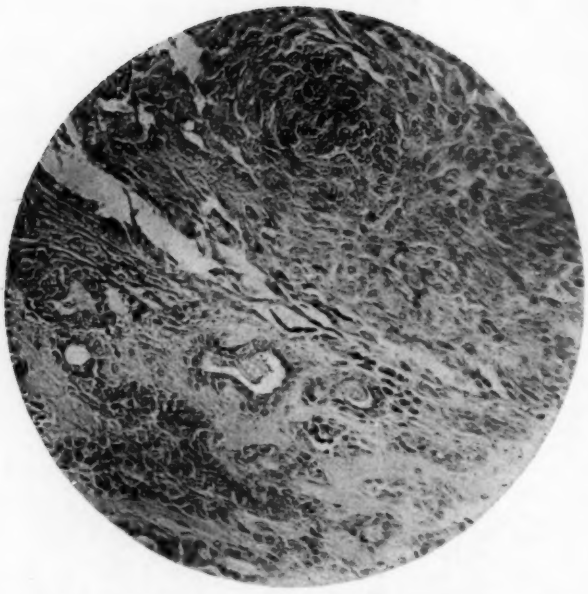

Fig. 4 (case 4).—Epithelium of squamous type, apparently infiltrating and merging with stroma.

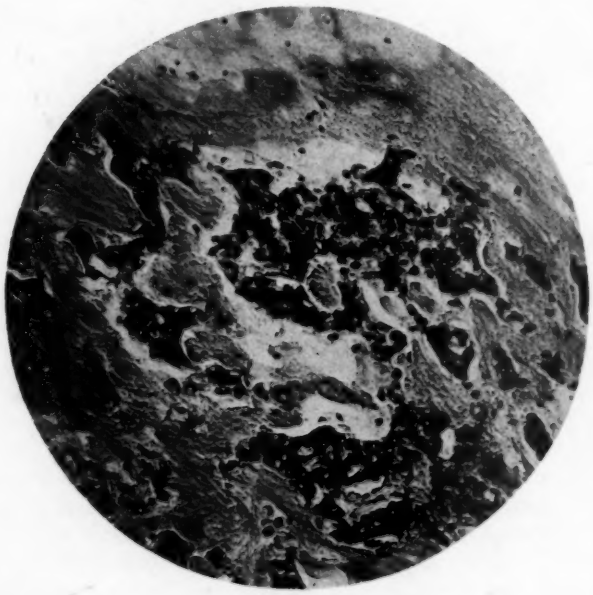

Fig. 5 (case 5).—Apparent infiltrative growth, but no merging of epithelium with hyaline stroma.

which its stroma, in the form of trabeculae of hyaline connective tissue, penetrated into its interior. Immediately covering these was a layer of cuboidal or frequently columnar epithelium; with this as a base, the superposed epithelial cells became progressively more polygonal or spherical until the central masses were composed of large cells of these types, with abundant cytoplasm. Mucoid connective tissue, cartilage, or squamous epithelium was not present. In the midst of the stroma, where this was abundant, were a few well formed tubules of glandular epithelium. This tumor has not been included among the mixed tumors as it apparently represents an adenoma.

CASE 7.—Case 7 was much like case 6, except that there was a more general penetration of the mass of the tumor by fine connective tissue trabeculae, and the epithelial cells were much more uniformly of columnar type. The result, in

Fig. 6 (case 6).—Adenoma of the palate.

general, was a more orderly picture of cellular hyperplasia than was presented by the material in case 6. In many instances the trabeculae showed such cellular disintegration that their fibrous character could only be surmised. Running through the center of the tumor was a large cleft, lined with cuboidal cells, in some places with a single layer of superficial flattened epithelium over these. No mucoid connective tissue, cartilage or stratified squamous epithelium was present. This, like case 6, apparently was an adenoma.

In the examination of this material, in addition to the routine staining, use was made of Kromayer's method, van Gieson's method and cresyl violet to demonstrate special features, such as intercellular bridges in cases 1 and 4.

Of the seven palatal tumors reported here, the first four are obviously to be regarded as mixed tumors, and they show the great diversity in the way of epithelial development which is to be found in this group of neoplasms. All four show certain features in common—the gradual transition from recognizable epithelial elements to those of unmistakable connective tissue, and,—closely linked with this—an apparently infiltrative growth of the epithelium. Case 1 illustrates this feature particularly well, as the squamous epithelium here shows all the features ordinarily associated with malignancy. In case 5, which is only doubtfully included among the mixed tumors, there

Fig. 7 (case 7).—Adenoma of the palate.

are suggestions of transition between connective tissue and epithelium in the way of occasional cells which are difficult to differentiate, but in general the two types of cell are clearly distinguishable. It shows, however, the same apparently infiltrative growth of epithelium which is present in the other four.

Malignancy in the mixed tumors of the palate is of far rarer occurrence than in those of the salivary glands; in the cases summarized in table 1, only two were found with histories of invasive or recurrent growth. It is possible to stress this fact too greatly, since most of the reports were made shortly after the removal of the primary tumor, and later recurrence may have escaped report, although this could be expected in at least some of the cases if recurrence had taken place.

In the case of the parotid tumors, it is the rather general consensus of opinion that, despite their microscopic evidences of malignancy, they become malignant in the clinical sense only when the growth has escaped either by extension or by trauma from the capsule which usually sur-

TABLE 1.—*Composition of Mixed Palatal Tumors*

Source	No.	Mucoid Connective Tissue	Cartilage	Gland Epithelium	Squamous Epithelium
Aimes	1	1	.	1	.
Alagna	1	1	.	?	1
Arzela	1	1	1	1	.
Baker	1	1	1	.	.
Barbezat	1	1	1	1	1
Berger	3	3	2	3	2
Boettger	1	1	.	1	.
Bogoljuboff	1	1	1	1	1
Bond	1	1	1	1	.
Chaput	1	1	.	1	.
Chiariello	1	1	.	1	.
Coenen	4	2	.	4	.
Coffin	1	.	.	1	1
Coley	1	1	.	1	.
Cordes	1	1	.	1	1
Cruet and Coustaing	1	?	.	1	.
Curling	1	.	.	.	1
Delafontaine	1	1	.	1	.
Eisenmenger	3	2	1	3	.
Escat	1	.	.	1	.
Finder	1	1	1	1	1
Freedman	1	1	1	1	1
Gouguenhein and Ripault	1	1	.	1	.
Halstead	1	1	.	1	.
Heron	1	1	1	1	.
Hoffmann	1	1	1	1	.
Ivy	2	1	.	2	.
Letenneur	2	2	.	2	.
Leto	1	1	.	1	.
Looser	1	1	1	1	1
MacCormac	1	1	.	1	.
Marsden	1	1	.	1	1
Massabauw	1	1	1	1	1
Mauclaire and Durrieux	1	1	1	1	1
Michaux	1	.	1	1	.
Michl	2	1	2	1	.
Moreau	1	.	1	?	.
Morestin	2	2	.	2	1
Morone	4	4	3	3	1
Morton	1	1	.	1	.
Negrie	1	.	1	1	.
New	1	.	.	?	1
Ott	1	1	1	1	.
Paget	6	3	1	6	5
Poncet	1	1	1	1	.
Raach	3	2	.	3	1
Reboul	1	1	1	1	.
Ritchie	1	1	1	1	.
Robinson	1	1	.	1	1
Roman	1	1	.	1	1
Rousseau	1	1	.	.	1
Shattock	1	1	1	1	.
Sturgis	1	.	1	1	.
Swynghedauw	1	1	1	1	.
Thaon	1	1	.	1	.
Tori	1	1	.	1	.
Trelat	1	1	1	1	.
Volkmann	4	3	.	4	3
Wood	2	.	1	2	.
Worms	3	3	.	3	1
Eggers	5	4	2	5	2
Total	92	.	35 (38%)	.	32 (34.8%)

rounds such a tumor. Such may be the explanation of the rare occurrence of malignancy in the palatal tumors, which causing much discomfort, readily recognized and easily removed, would ordinarily receive early surgical intervention. It must be emphasized, how-

ever, that from the morphologic point of view alone, practically all of the palatal tumors would be adjudged as malignant; from the clinical point of view, almost none.

In table 1, teratomatous tumors of obvious character have been omitted intentionally, neoplasms which show finished structures, as for instance hair follicles, being considered of that sort. They are less frequent in the palate than in many other locations, and as regards derivation probably represent a somewhat different problem from that of the tumors under consideration. Ordinarily, unlike the mixed tumors which occur almost exclusively during adult life, they appear at an early age, although at least one case, that of Garel, is an exception to this rule. At the other end of the scale, adenomatous tumors offered some difficulty. Here the criterion for exclusion was in part the character of the stroma or, in some cases, the finished character of the epithelial structures.

TABLE 2.—*Composition of Mixed Tumors of the Parotid and Submaxillary Glands*

Source	No.	Mucoid Connective Tissue	Cartilage	Gland Epithelium	Squamous Epithelium
Böttner	25	25	13	25	9
Ehrich	26	..	15	..	14
Hinsberg	9	6	4	..	2
Nasse	24	23	11	18	6
Perochaud	14	11	4	12	1
Speese	9	..	6	..	4
Volkmann	28	28	11	26	8
Wood	48	..	14	..	12
Total	183	.	78 (42.6%)	.	56 (30.5%)

Table 2 represents a summary of a number of the more extensive reports on parotid and submaxillary mixed tumors, for purposes of comparison with the results of table 1 as regards the more usual tissue elements. In compiling this table, reports of isolated cases were not considered, although had they been the number of cases represented would be materially increased. It was believed that tumors of unusual or of unusually complex composition would be more likely to be reported separately, and so would be less representative than a series of collected cases reported as a whole. In the analysis of the reports for tissue elements, these had to be inferred in part from the descriptions of the tumors and occasionally from the illustrations. This applies to both tables. When a tissue was reported as doubtfully present—this applies particularly to cartilage—in the compilation it is reported as present, for purposes both of simplicity and of uniformity.

There are few phases of neoplastic growth which have evoked greater diversity of opinion as to derivation than this group of oral

and salivary tumors. They have been viewed as resulting from embryonic displacement, the exact manner and time varying with the writer and his material; they have been viewed as "cylindromas," (Billroth), sarcomas (Kaufmann) and endotheliomas (Franke, Nasse, Volkmann and Hansemann). More recently a view directly reversed to the last mentioned has been widely accepted, and they are regarded by many pathologists as being of purely epithelial derivation.

The theory of embryonic displacement, as advocated by Paget, Guleke, Wood, Herxheimer and others, would account most satisfactorily for these tumors if it were not for the fact that occasionally they show a gradual mergence into normal glandular structures, and that usually they show an intimate blending of parenchymatous epithelium and stroma to the point where it is impossible to determine where the one ends and the other begins. This blending extends even to the finer details in the form of cellular projections and fibrils which appear to unite definitely cells of undoubted epithelial character with others just as certainly stromatous. The earlier reflection of these apparent transitions was the classification of these tumors as endotheliomas, a view rather widely accepted until it was shown, by Hinsberg and later by others, that in many specimens the parenchyma occurred in the form of unmistakable glandular or squamous epithelium. At present the theory of the endothelial character of these tumors has been almost universally abandoned. But with the recognition of their epithelial contents there was simply a shifting of the dilemma, and to explain the apparent transition from epithelium to connective tissue there was advanced the theory of actual metaplasia of epithelium into mucoid connective tissue or cartilage. Even this theory took several divergent forms. Ehrich believed that the metaplasia was primarily due to the secretion of seromucous material by the parenchymatous cells, under the influence of which their detached fellows assumed the forms of the stromatous elements. Krompecher took the view that there was an actual metaplasia of epithelium to stroma, and based this, not only on morphologic, but on embryologic, grounds as well. He suggested that the cells of these tumors simply retain the property of early general developmental potency. A somewhat similar view was taken by Forman and Warren, who called attention to the fact that throughout a wide range of vertebrates there is an early development of cartilage from the ectodermal cells of the anterior part of the neural crest.

This view in its simplest form is not incompatible with the theory of embryonic displacement, but unfortunately for this apparent harmony, a rather considerable number of parotid and submaxillary tumors have been described in which the tumor passes imperceptibly into normal glandular tissue, and so is apparently derived from that source.

Also, it is in a number of tumors of this description that the most striking morphologic evidence has been found of epithelium-connective tissue metaplasia. So Desmarest and Masson, Masson and Peyron, and Fraser, believed that these tumors, occurring in the salivary glands, may be derived by metaplastic processes involving the development of the neoplastic epithelium from that of the normal gland, and of the connective tissue from the epithelium of the tumor. In the case of the palatal tumors, a similar process is postulated from the mucous glands of this region.

It must be conceded that the morphologic evidence for this view in the case of certain selected tumors is striking; but there are several related phenomena which cast some doubt on the validity of evidence of this sort. As regards the apparent transition from normal glandular epithelium to that of the tumor, it has been shown both by Carraro and Fraser that after injury to the salivary glands their epithelium undergoes a change of structure and grouping to that of an adenomatous character. Since it is in the uncapsulated mixed tumors that the apparent transition is observed, it is found in exactly the circumstances in which the tumor would be most likely to traumatize the gland itself, and so to induce the gradual change of structure. Concerning the apparent transition from epithelium to stroma, that is frequently observed where epithelium is in especially close association with mucoid connective tissue. Krompecher, for instance, regarded the mixed salivary tumors as coming under the same classification as his "muco-hyaline basal cell carcinomas"—rare "basal-cell" carcinomas in which there was a stroma of mucoid type, in which he found the same apparent transitions. Among the material at this school is an adenocarcinoma of the ovary with excessive mucoid stroma in which most of the epithelium occurs in the form of well developed and sharply delimited tubules, but with occasional small areas of definitely infiltrative growth. In the latter areas the epithelial cells, clearly recognizable as such by their distinctive cytoplasmic stain, apparently merge with the cells of the stroma both by projecting processes and by means of fine intracellular fibrillae. In other words, this apparent merging of epithelium and stroma appears to be a fairly general phenomenon when there is an invasive growth of epithelium into a stroma bathed in an excess of mucinous fluid, and may with some probability be explained on the basis of infiltrative growth plus saturation with this fluid. The same explanation may be applied to the apparent transition from epithelium to cartilage, the dissolved colloid in that case being of chondromucoid character. It is perhaps of some significance in this connection that in the adenomas of the palate as illustrated by cases 6 and 7, in which there is no mucoid stroma, there is no evidence of this transition, and in case 5 very little. As bearing on Ehrich's hypothesis that the epi-

thelial secretion is the determining factor in the production of the peculiar stroma, figure 8 is inserted; this shows a mixed parotid tumor in which both mucoid and cartilaginous stroma occur together with epithelium purely of squamous type and scarcely to be regarded as having secretory function.

While it is suggested that the metaplasia from epithelium to connective tissue in these tumors may be more apparent than real, the principle of metaplasia or heteroplasia appears to be essential to the explanation of the various tissue elements within the same class. In case 1 there is every morphologic evidence that the two types of

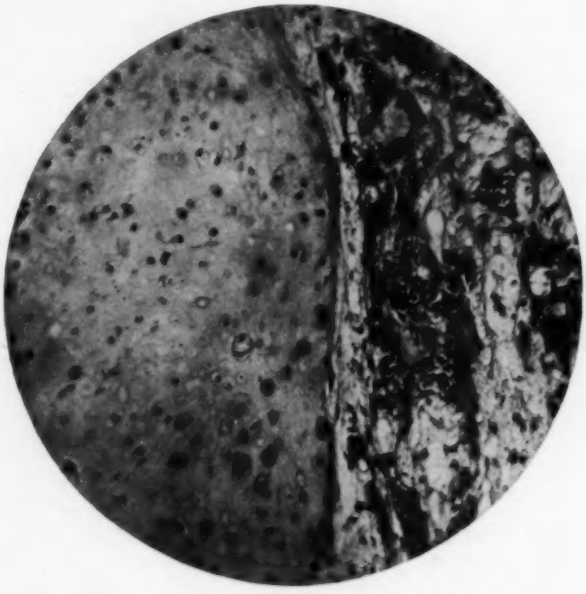

Fig. 8.—Mixed tumor of the parotoid gland; epithelial elements of purely squamous character.

squamous and columnar epithelium originate from the same basis, a simple undifferentiated cuboidal epithelium bearing a close resemblance to that of the embryonic pharynx. A considerable number of tumors of this general region have been reported in which similar or even more striking evidence of metaplasia or heteroplasia has been found, most notably an adenoma of the parotid reported by Masson and Berger. In figure 9, showing at a higher magnification a portion of the material of case 1 in which there is this apparent metaplasia into stratified squamous epithelium, the particular epithelial pearl illustrated has evidently been formed on the foundation of an inclusion, in a manner resembling that described in tissue specimens by Erdheim and

in experimental material by Loeb. Probably no particular significance is attached to this, as it is the only structure of the sort in which this was seen.

Also as regards the derivation of the cartilage, there is reason to consider it as developing from the mucoid connective tissue by a process strongly suggestive of its formation in embryonic life. In practically all of the mixed tumors it is impossible to determine everywhere the boundaries between mucoid connective tissue and cartilage, and in many of them their consistency is distinctly cartilaginous, even though the microscope reveals few or no cartilage cells within the matrix.

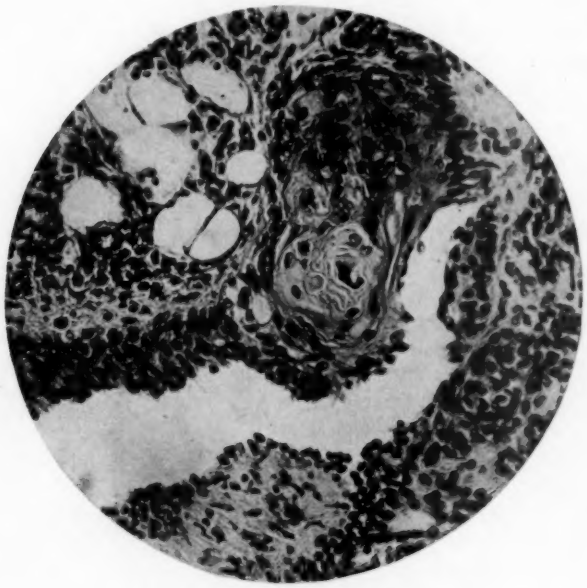

Fig. 9 (case 1).—Epithelial metaplasia.

In view of the fact that the apparent derivation of these tumors from preexisting glands and the close association or apparent blending of parenchyma and stroma are open to explanation on other grounds than that of metaplasia from a common source, the theory of embryonic displacement would seem to remain the most adequate explanation of their origin. The initiation of this displacement could probably occur at different periods of development and specialization, and in this way, at least one factor would be introduced to account for their varied morphology. It had been hoped that some light might be thrown on this particular phase of the problem by the analysis of the contents of a large number of tumors of the palate and by comparison of this

with similar data pertaining to the parotid and submaxillary glands. To the extent that the results of these analyses show a greater incidence of cartilage in the parotid and submaxillary tumors as compared with those of the palate—42.6 per cent and 38 per cent, respectively—and a somewhat lower incidence of squamous epithelium—30.5 per cent for the former, 34.8 per cent for the latter tumors—they would support the theory of embryonic displacement, since the palate, formed at a later period than the salivary glands, would be less likely to contain embryonic cartilage and would be more likely to contain epithelial elements destined to form stratified squamous epithelium. But the disparity in the results is so slight, and there is so much variation in the several series of tumors of the parotid gland, that it must be confessed the evidence is not particularly valid.

The occurrence of tumors of this sort with some frequency in the lacrimal glands has been adduced by Warthin and by Verhoeff as evidence against the theory of embryonic displacement. Obviously, branchial cartilage can scarcely enter into tumors in this location. There is, however, a possible nearer source of cartilage to be considered, that of the developing ethmoid, between which and the gland anlage the lacrimal bone is interposed only at a later period. There can be no doubt that such displacement must operate in certain of the facial mixed tumors. For example, I have recently received for examination a chondro-epithelial tumor removed from the region of the postauricular lymph glands under the tentative diagnosis of tuberculous lymphadenitis. There was no apparent involvement of the parotid. Wood includes a similar case in his material.

It has not seemed advisable to introduce an exhaustive discussion of the extensive literature which has accumulated on the subject of the mixed tumors. The ground has been covered several times by Wood, Wilson and Wills, and with exceptional completeness by Heineke, and by McFarland principally from the period of Heineke's report to 1926.

SUMMARY

The five mixed tumors of the palate reported here show marked diversity of structure; they are all alike in that they show infiltrative growth of the epithelial elements, and in all except one, there was an apparent merging of epithelium into stroma.

The infiltrative epithelial growth in these tumors does not appear to be indicative of malignancy in the clinical sense.

It is possible to explain the apparent origin of certain tumors of this sort from normal glandular epithelium on the basis of injury to the gland by the growing tumor, and the apparent metaplasia of epithelium into stroma as a feature of infiltrative growth into mucoid

connective tissue; so that it would seem that the theory of embryonic displacement remains the most probable explanation of these tumors, particularly as they sometimes occur in regions where such displacement would appear to be essential.

An analysis of 92 published reports of palatal tumors, as compared with 183 tumors of the parotid and submaxillary glands, shows a somewhat lower incidence of cartilage and a higher incidence of stratified squamous epithelium in the former. This could be expected if the displacement theory is correct, in view of the later development of the palate. But in view of the variation in the reported series of salivary tumors, this evidence cannot be regarded as decisive.

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THE ATTRACTION OF LYMPHOCYTES BY HOMEOTOXINS *

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In a series of investigations from this laboratory, it was shown that it is possible to determine, in a quantitative manner, the similarity, or lack of similarity, between the individuality differentials of host and donor of a transplant, by estimating the intensity and the time or appearance of lymphocytic infiltration around and in the transplanted piece of tissue, and, furthermore, by grading the intensity of the invasion of the latter by connective tissue cells and the tendency of the cells to produce dense fibrous tissue which presses on and contributes to the injury and destruction of the strange tissue.[1]

Under ordinary conditions the lymphocytes are carried to the transplant mainly by way of the lymph vessels of the host. Often, the latter are so densely packed with lymphocytes that they appear as though they are injected with a dye, and, on this account, they can be clearly recognized. From here the lymphocytes migrate and move into the transplant which they thus help to destroy. It is probable, also, that they migrate from the blood vessels, although this process, if it occurs at all, seems to play a minor rôle in most cases.

It was of interest to inquire whether lymphocytes of the host tissue may also be attracted to the transplant directly by means of homeotoxins given off by the latter, if a tissue rich in lymphocytes and possessing the differential of the host (being a part of the latter) should happen to be located near the homeotransplant. One way by which such a condition might be brought about would be by transplantation of the homeotissue into the direct vicinity of a lymph gland of the host; but this seems to be difficult to accomplish, and, furthermore, it is doubtful whether the dense capsule surrounding the lymph gland would permit the lymphocytes to migrate in large masses toward the transplanted piece. There is, however, another method which promises better results. If one transfers into a subcutaneous pocket of a guinea-pig a piece of lymph gland tissue derived from the host, and places, in close approximation to it in the same pocket, a piece of xiphoid cartilage from another nonrelated guinea-pig, it is conceivable that the homeocartilage will attract the

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1. Loeb, Leo.: Biol. Bull. **40**:179 (March) 1921 (references to earlier papers of this series are found here); Am. J. Path. **2**:99 (March) 1926; ibid. **2**:301 (July) 1926.

lymphocytes from the autotransplanted lymph gland, which will, at least in part, survive in its new location. There would be justification for the conclusion that such a process does occur, if one should observe that the lymphocytes, which in time begin to surround and to invade the homeotransplant, can be traced directly to the neighboring lymph gland, instead of being carried to the transplant exclusively by way of the lymph and blood vessels. In the former case, strands of lymphocytes should connect the neighboring lymph gland and the homeotransplanted cartilage, and the part of the cartilage that is adjoining the lymph gland should show a more dense infiltration with lymphocytes than parts more distant. Furthermore, one should expect that, in addition to the infiltration with lymphocytes from the local source, an infiltration of cells which have been carried to the homeotransplant through the general circulation should take place.

In each of these experiments guinea-pigs obtained from different sources were used, so that it was reasonably certain that the donor and host of the transplanted tissues were not closely related. The guinea-pigs were males, weighing approximately from 400 to 500 Gm.

The operative technic was as follows: An incision, about 1 inch (2.5 cm.) long, extending from the middle of the cartilage to the abdomen, was made over the xiphoid cartilage of the animal serving as host; subsequently, two subcutaneous pockets were formed, one on either side of the midline. A lymph node was then excised from the cervical region of the same animal, and one half of the lymph gland was transferred into each pocket. If it was desired to use cartilage of the host guinea-pig, a piece was taken from the xiphoid and placed in approximation to the lymph node. In case of homeotransplantation, cartilage was taken from an unrelated guinea-pig and likewise transplanted in close apposition to the lymph node. The pockets and skin were then closed by means of silk sutures.

A rather extensive series of experiments was carried out, but only those in which the pieces of lymph gland and cartilage remained in contact with each other could be used; the number of successful experiments of this kind was limited.

As to the results obtained, the autotransplanted lymph glands were, in general, well preserved at the time of examination, although in some cases, a diminution in lymphocytes was noticeable and an increase in connective tissue in the transplants, a condition which was, perhaps, due to the organization of necrotic areas which developed in the center of the lymph gland in the first few days after operation.

In autotransplantation of the cartilage, the lymph gland and cartilage usually showed well defined outlines and were separated from each other by a zone of connective tissue. On the other hand, in homeotransplanta-

tion of the cartilage it was clearly seen in favorable sections that strands of lymphocytes extended from the lymph gland to adjoining parts of the cartilage. At these points the lymphocytic infiltration around the cartilage was usually densest, while in other places it was less dense or lacking. These observations render it at least probable that a direct migration of lymphocytes took place from the lymph gland to the homeotransplanted

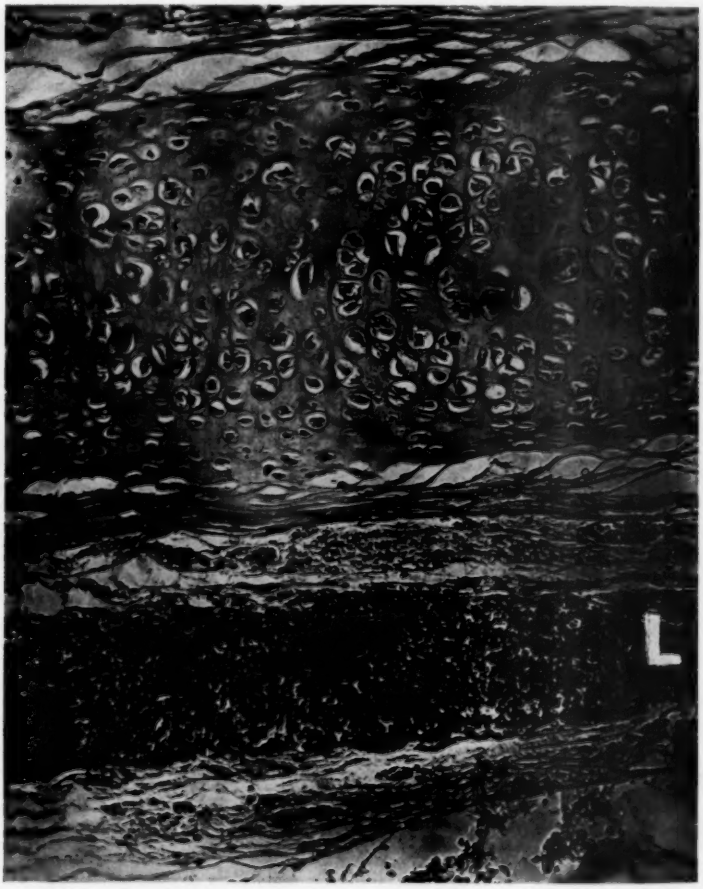

Fig. 1.—Twenty-seven days old autotransplants of cartilage and lymph gland. In this and the following figures, *C* indicates cartilage; *L*, lymph gland.

cartilage. Here these cells penetrated into the fat and connective tissue surrounding the cartilage and also into the latter itself, in places where it was cellular and, therefore, sufficiently soft to permit such invasion. In some experiments the technic employed was somewhat different: Without removing and transplanting the lymph gland of the host, an incision was made into it, and the cartilage was then placed in the center of the

lymph gland. If this procedure was successful, the lymphocytes surrounded and invaded the homeotransplant on both sides.

The photomicrographs illustrate my results:

Figure 1 represents a 27 day old autotransplant of cartilage and lymph gland. Both cartilage and lymph gland are well preserved and well approximated to each other. Capillaries are numerous in areas in

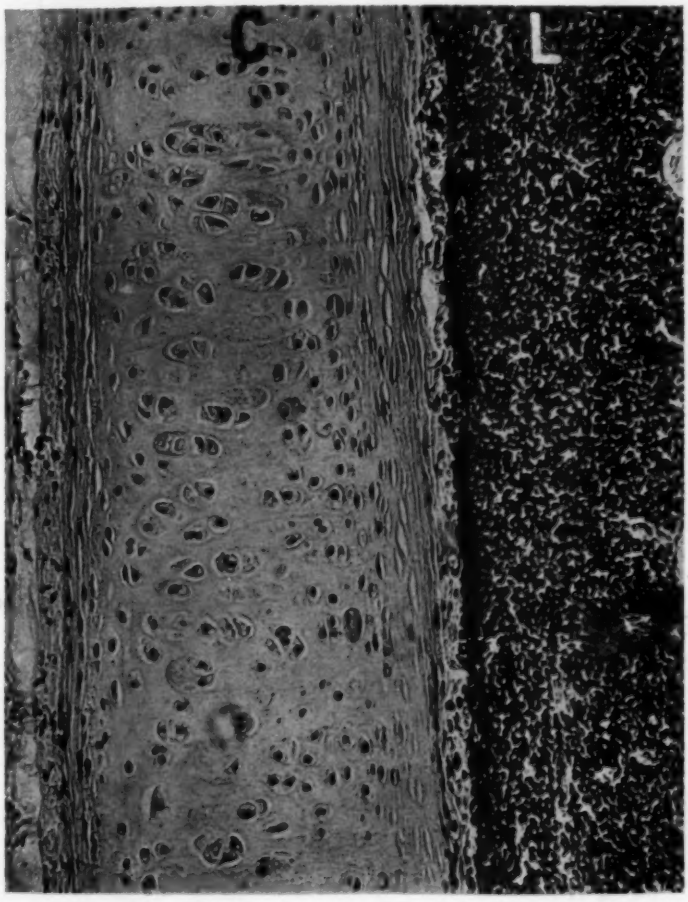

Fig. 2.—Thirty days old autotransplants of cartilage and lymph gland.

the connective tissue that separates lymph node and cartilage. Some scattered lymphocytes can be seen in the fibrous tissue around the cartilage, but a real invasion of cartilage by lymphocytes has not taken place, both organs being well delimited.

Figure 2 reproduces a 30 day autotransplant of lymph gland and cartilage. The approximation of both organs, which are well preserved,

is perfect. A few lymphocytes are seen in the connective tissue surrounding the cartilage, but invasion of the cartilage by lymphocytes does not occur.

The results are different if one combines with an autotransplantation of lymph gland a homeotransplantation of cartilage. The results in such experiments are illustrated in figures 3, 4, 5, 6 and 7.

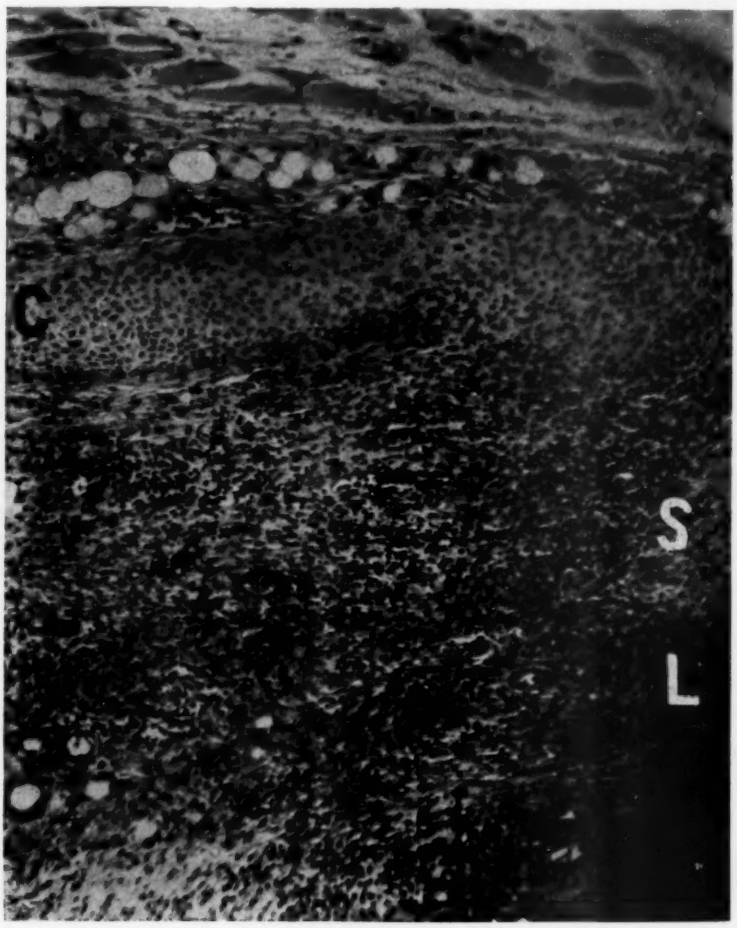

Fig. 3.—Twenty days old autotransplants of lymph gland and homeotransplant of cartilage. In this and the following figures, *S* indicates lymphocytes.

Figure 3 shows the lymph gland fairly well approximated to the cartilage twenty days after transplantation. Lymph gland and cartilage are connected by strands of lymphocytes which extend from the lymph node and invade the adjoining portion of the cartilage. Farther away from the lymph node, the cartilage transplant is almost free from lymphocytic infiltration.

Figure 4 is a higher magnification of an area in figure 3. The lymphocytes are seen moving from the lymph gland in connected strands, in the direction of the cartilage, and here they invade the more cellular and, therefore, softer portions of the cartilage.

Figure 5 represents an autotransplant of a lymph gland and a homeotransplant of cartilage. At one end of the cartilage transplant, masses of

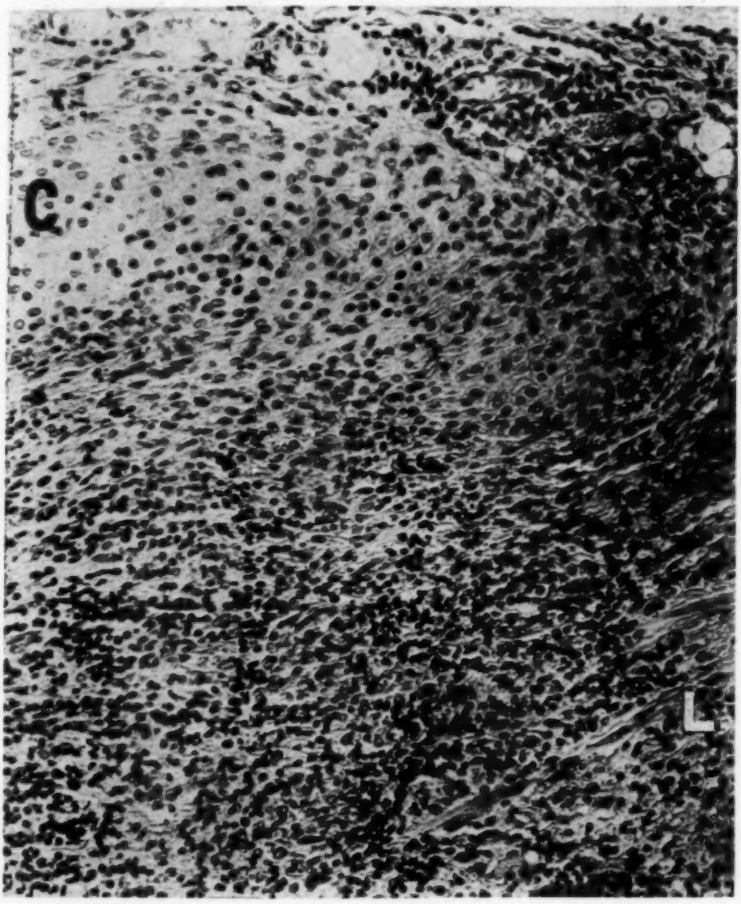

Fig. 4.—Area of figure 3 shown at higher magnification.

lymphocytes, coming from the nearby lymph gland, invade the cartilage tissue which was injured during the process of transplantation. In places farther distant from the lymph node, infiltration with lymphocytes is almost lacking.

Figure 6 shows the area of invasion in figure 5 at a higher magnification; it is evident that the lymphocytes migrate from the lymph gland

into the adjoining end of the cartilage, and also into the surrounding perichondrium.

Figure 7 represents a 40 day old homeotransplant of cartilage which has been placed in the middle of an autotransplanted lymph gland. At various points, lymphocytes coming from the lymph gland tissue situated on both sides of the cartilage markedly invade the cartilage.

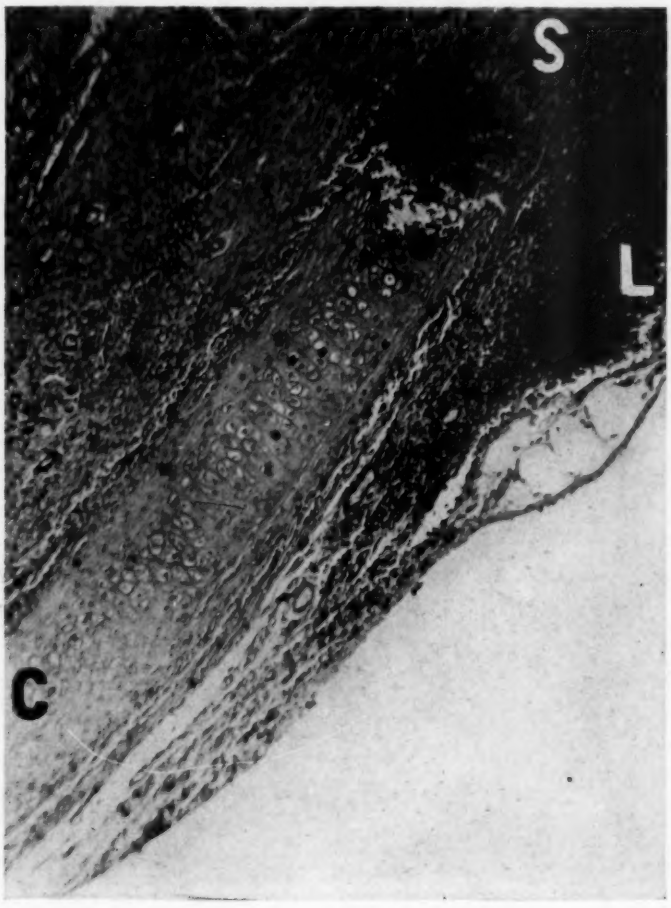

Fig. 5.—Twenty-three days old autotransplant of lymph node and homeotransplant of cartilage.

CONCLUSIONS

These experiments prove that the lymphocytes of a lymph gland adjoining homeotransplanted cartilage may be attracted by the homeotoxins given off by the cartilage directly; that neighboring lymph tissue may thus act as a source of supply for the lymphocytes which are necessary for the invasion of the transplant, and that the accumulation of

lymphocytes around and in the transplant does not, therefore, necessarily depend merely on the distant action of the homeotoxins affecting the lymphatic circulation.

These experiments indicate that in this accumulation of lymphocytes around a homeotransplant, one has, in all probability, to deal with a chemotropic reaction. In this connection, reference is made to experi-

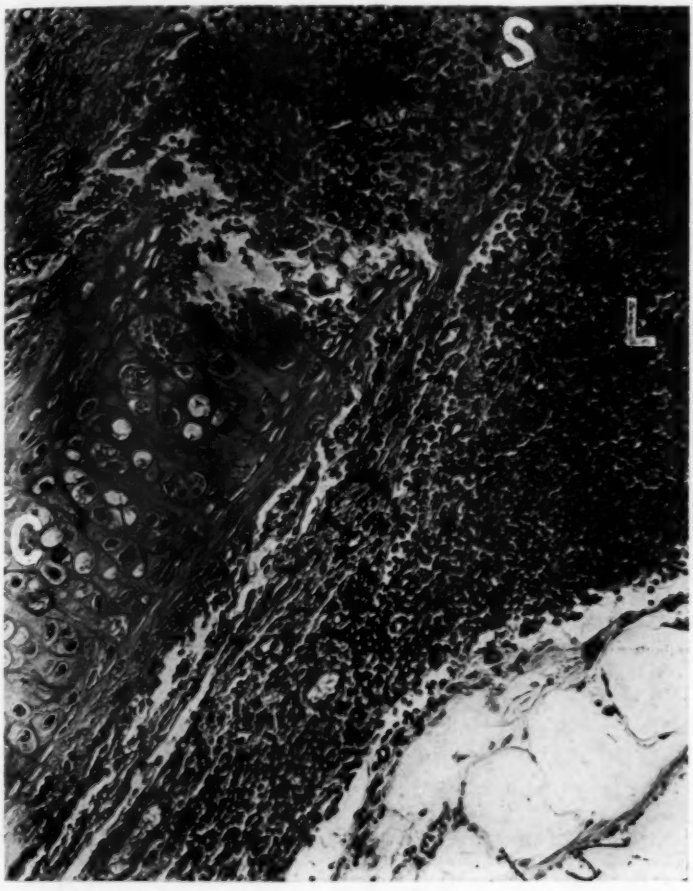

Fig. 6.—Area of figure 5 shown at higher magnification.

ments by Murphy [2] in which he found that the tolerance for tumors or normal tissues after heterotransplantation into the allantois or brain of the chick and into the brain of rats can be abolished by the subsequent placing of a piece of spleen or bone marrow into the organ used for transplantation. As a result of the action of spleen or bone marrow an

2. Murphy, J. B.: Monographs, Rockefeller Institute, 1926, no. 21.

immunity developed in these cases against the heterotransplant, and this immunity was indicated by the typical infiltration with lymphocytes and connective tissue observed around the transplants. In the experiments one has to deal not with an immune reaction but with a local reaction on the part of the lymphocytes against the transplant under the influence of homeotoxins given off by the latter, and with the subsequent invasive

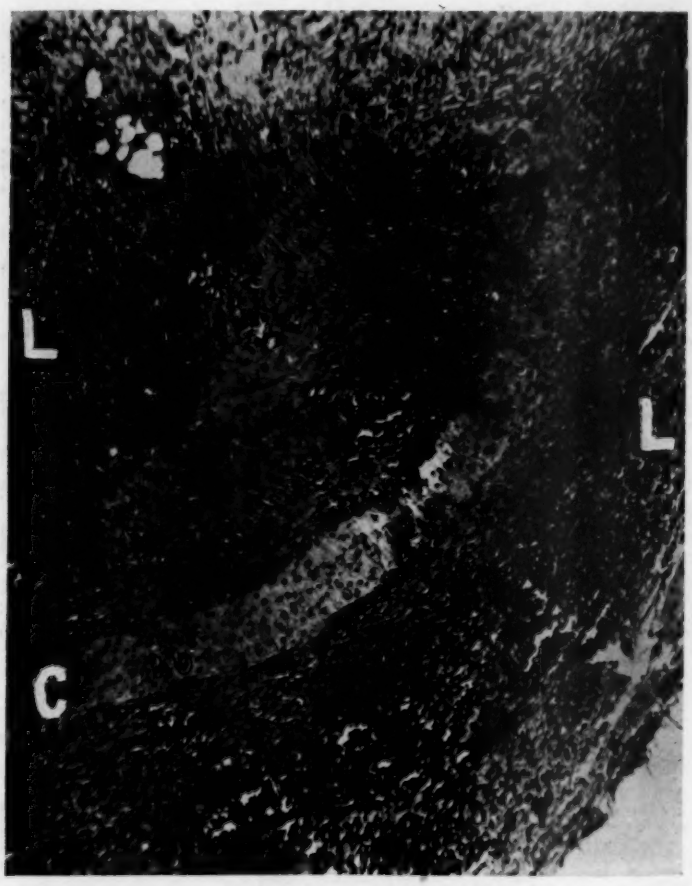

Fig. 7.—Forty days old autotransplant of lymph gland and homeotransplant of cartilage. The cartilage has been placed in the center of the lymph node.

and destructive action which the lymphocytes exert on the homeotransplant. The lymphocytes remain inactive toward autotransplanted cartilage, because these tissues do not give off substances which attract the lymphocytes.

SUMMARY

1. If one carries out in the same animal an autotransplantation of cartilage and one of lymph gland, and places both transplanted tissues in

close proximity to each other, the lymphocytes of the lymph node remain inactive, because the individuality differentials are identical in both tissues and the autosubstances do not exert a stimulating action on the lymphocytes.

2. If by the same method one combines an autotransplanted lymph node and a piece of homeotransplanted cartilage, one may, under favorable conditions of experimentation, observe a definite migration of the lymphocytes from the lymph gland toward and into the transplant; in this case, the individuality differential of the cartilage differs from that of the lymph node, and, as a result of this difference, homeotoxins develop which attract the cells from the lymph node in the direction of the cartilage.

AUTOPLASTIC LYMPH NODE AND THYMUS TRANSPLANTS

COMPARATIVE STUDIES *

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Studies by numerous investigators on the histogenesis of the thymus gland have failed to clear up the origin and biologic significance of the small thymic cell. The followers of His,[1] Hammar,[2] Maximow[3] and others[4] maintain that these cells arise from mesenchymal cells that have migrated into the thymus anlage. The school of Kölliker,[5] Beard,[6] Mauer[7] and Stöhr[8] believes that these cells are derived from the original epithelium of the thymus.

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* From the Division of Laboratories, Montefiore Hospital.

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2. Hammar, J. A.: The New Views as to the Morphology of the Thymus Gland and Their Bearings on the Problem of the Function of the Thymus, Endocrinology **5**:543 and 731, 1921.

3. Maximow, A.: Untersuchungen über Blut und Bindegewege: 2. Ueber die Histogenese der Thymus bei Säugetieren, Arch. mikr. Anat. **74**:527, 1909; Untersuchungen über Blut und Bindegewebe: 4. Ueber die Histogenese der Thymus bei Amphibien, ibid. **79**:560, 1912; Untersuchungen über Blut und Bindegewebe: 5. Ueber die embryonale Entwicklung der Thymus bei Selachieren, ibid. **80**:39, 1912.

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In order to secure additional data concerning the origin of these cells, the method of autoplastic thymus transplantation, with careful histologic studies of the daily regenerative changes which take place in the growing transplants, was utilized.[9] These studies revealed that regenerative changes begin about forty-eight hours after the transplant was made and result in a fully differentiated thymus by the fourteenth day. The most striking feature of thymus transplant regeneration is the rapid almost complete regeneration of the reticulum before any small thymic cells appear, followed by the appearance of widely scattered groups of small thymic cells throughout the reticulum. These groups enlarge, fuse and finally become densest in the so-called cortex. It was concluded from these experiments that the small thymic cell in the rat arises from the reticular epithelium. In an effort to gather further evidence on this much mooted question the regeneration of a series of lymph node transplants has been studied and compared with transplants of the thymus in rats of the same age, sex and strain.

To our knowledge, detailed or extensive studies are not available concerning the successful transplantation of lymph nodes. In our studies, young albino rats were used. Pieces of inguinal lymph nodes, approximately 6 mm. in diameter, were planted into prepared pockets in the abdominal wall. The presence of infection in these nodes in young rats is infrequent, and in our series less than 5 per cent of the lymph nodes were infected. Over 95 per cent of our transplants of inguinal lymph node regenerated.

METHODS

In this work young tame albino rats, varying in age from 2 to 4 months, were used. These rats were raised in the laboratory. The methods of preparing the animals for transplantation have been described in a previous communication.[8] Lymph nodes in the groin were exposed, separated, with as little trauma as possible, from the surrounding tissue, cut into pieces approximately 6 mm. in diameter and immediately inserted into separate, previously prepared pockets in the abdominal muscle. Great care was exercised to avoid hemorrhage into these pockets, and, if hemorrhage occurred, a new pocket was made. The site of the transplants was indicated by the closing of the mouth of the pocket with a black silk suture. Three transplants were usually inserted into each animal.

Preceding the removal of the transplants, the animal was anesthetized with ether; afterward it was killed, and a complete autopsy was done. The transplants were fixed in Bouin's solution, Kohn's solution or 10 per cent formaldehyde. The tissues were embedded in paraffin and cut serially. The sections were stained with hematoxylin-eosin, Heidenhain's iron hematoxylin, Flemming's triple stain, the Pacini stain for reticulum and Van Gieson's stain.

9. Gottesman, Jessie M., and Jaffe, H. L.: Studies on the Histogenesis of Autoplastic Thymus Transplants, J. Exper. Med. **43**:403, 1926.

PRESENTATION OF DATA

This study is based on the examination of sixty-four lymph node transplants removed from twenty-three young rats and fixed and stained by the methods described. For purposes of comparison, eighty-five thymic transplants were made in a similar manner in twenty-eight young

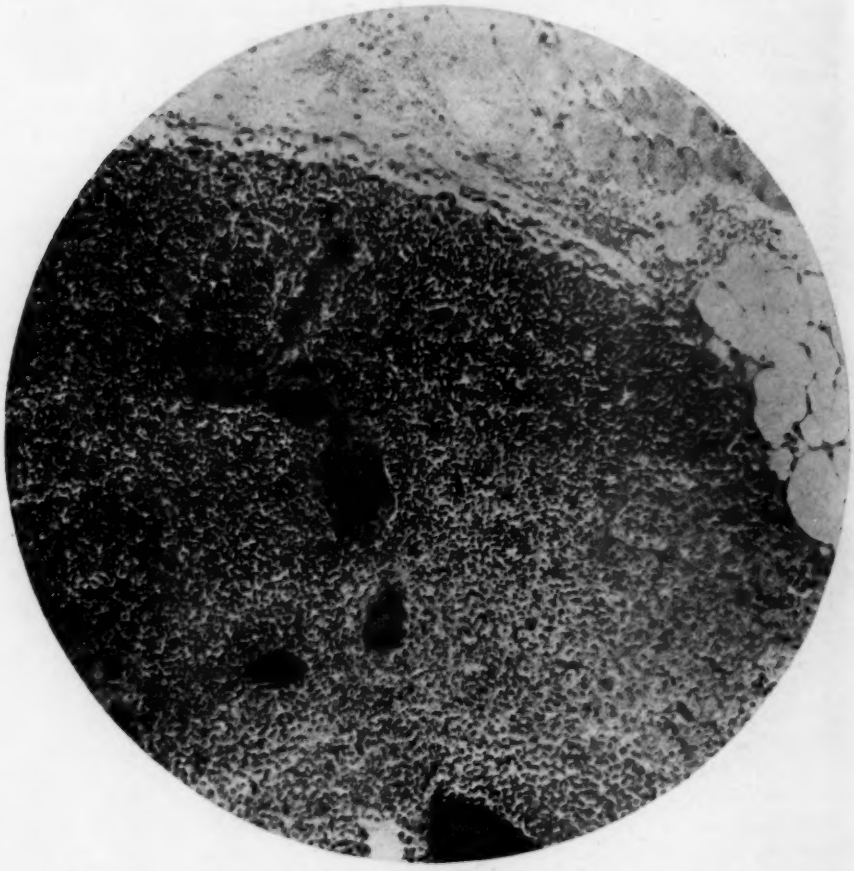

Fig. 1 (twenty-four hours).—Irregular clumping of small lymphocytes with pyknosis and karyorrhexis. Blood vessels markedly dilated and congested.

rats. The lymph node transplants were examined at approximately twenty-four hour intervals until the sixteenth day. A description of the successive stages of degeneration and growth of the transplants follows:

Twenty-Four Hour.—A moderate inflammatory reaction was observed in the muscle fibers about the transplant, with edema of the surrounding tissue (fig. 1). The small lymphocytes of the transplant were agglutinated in clumps, and many

of their nuclei showed pyknosis and karyorrhexis, except at the periphery where there was still a zone of well preserved lymphocytes. The nuclear débris was collected in small masses throughout the interior of the transplant. The reticular cells showed a corresponding disintegration, most marked in the central area. Almost the entire transplant was invaded by numerous polymorphonuclear leukocytes which surrounded the large masses of nuclear material. The leukocytes were actively phagocytic and many were filled with nuclear débris. The vessels

Fig. 2 (forty-eight hours).—Extensive central necrosis of the transplant. Beginning proliferation of the reticular cells with formation of many small lymphocytes in the outer zone.

at the periphery of the transplant were dilated and engorged, and contained a large number of polymorphonuclear leukocytes. There was no evidence of hemorrhage into the transplants. Numerous capillaries had appeared, particularly in the center of the transplant. Edema was present in the surrounding muscle fibers. Between the muscle fibers were seen large numbers of lymphocytes which had probably wandered out from the transplant.

Forty-Eight Hour.—Extensive destruction had taken place in both the lymphocytes and the reticular cells, the most pronounced disintegration being in the center of the transplant (fig. 2). The reticular cells at the periphery of the transplant had begun to proliferate, increase rapidly by mitotic division and extend in finger-like processes toward the center of the transplant. They varied in size and shape—some were spindle-shaped and some were round. Many small lymphocytes were present in the outer zone of the transplant, in which the most active

Fig. 3 (three days).—Extensive reticular cell regeneration. Small central area of necrosis still present. The small lymphocytes are most numerous in the outer zone.

proliferation of the reticulum occurred. These appeared to arise from the proliferating reticulum. Numerous transitional forms from the reticular cells to lymphocytes were discernible. Newly formed blood vessels surrounded and extended into the transplant. Few lymphocytes were seen in the muscle around the transplant.

Three Day.—Reticular cells had regenerated and overgrown the entire transplant except for the central area of necrosis (fig. 3). At the same time, a large

number of lymphocytes were seen in the outer zone of the transplant. Transitional forms between fully developed lymphocytes and large oval reticular cells could be distinguished. The small lymphocytes were most numerous in that portion of the transplant in which the most active proliferation of the reticulum occurred and seemed to develop from the reticular cells. An area of necrosis was still present in the center of the transplant. A few polymorphonuclear leukocytes were still seen in the transplant and in the surrounding muscle.

Fig. 4 (four days).—Complete regeneration of the reticulum, except for a small central area of necrosis. The lymphocytes in the outer zone have increased in number.

Four Day.—At this stage, complete regeneration had taken place in the reticulum; it was hyperplastic and vascular (fig. 4). A great number of small lymphocytes were scattered throughout the transplant, but were densest in the peripheral zone. In the center a small area of necrotic tissue and cellular débris was still to be seen. The surrounding tissue did not show an inflammatory reaction.

Five Day.—Further regeneration had occurred, and the small lymphocytes were closely packed and masked the reticulum, especially in the outer zone of the transplant. A small area of necrosis was still present in the center of the transplant.

Six Day.—Extensive regeneration of the reticular elements was observed, and numerous transitional forms were seen (fig. 5). Large numbers of small lymphocytes were scattered throughout the reticulum. The small focus of necrosis within

Fig. 5 (six days).—Dense accumulations of lymphocytes in the outer zone of the transplant. Foreign body giant cells surround the small central area of necrosis.

the center of the transplant was almost completely surrounded by giant cells. The giant cells appeared to be formed by the fusion of reticular cells, and although they only occasionally resembled the typical foreign body giant cell, were, nevertheless, considered as a foreign body giant cell reaction of the reticular elements to the focus of necrosis. These giant cells possessed from six to eighteen nuclei. The nuclei were placed around the edge in some instances, as in foreign body giant cells, but in most of the cells they were scattered throughout the entire giant

cell. In one area, the reticulum showed extensive pleomorphism near the giant cell formation.

Seven Day.—A well defined capsule was seen about the transplant, now closely resembling a normal lymph node. The reticular cells were almost completely masked, as a result of overcrowding by the small lymphocytes.

Eight Day.—The sections showed regenerative transplant areas with the beginning formation of germinal centers (fig. 6). As in the preceding stages, the small

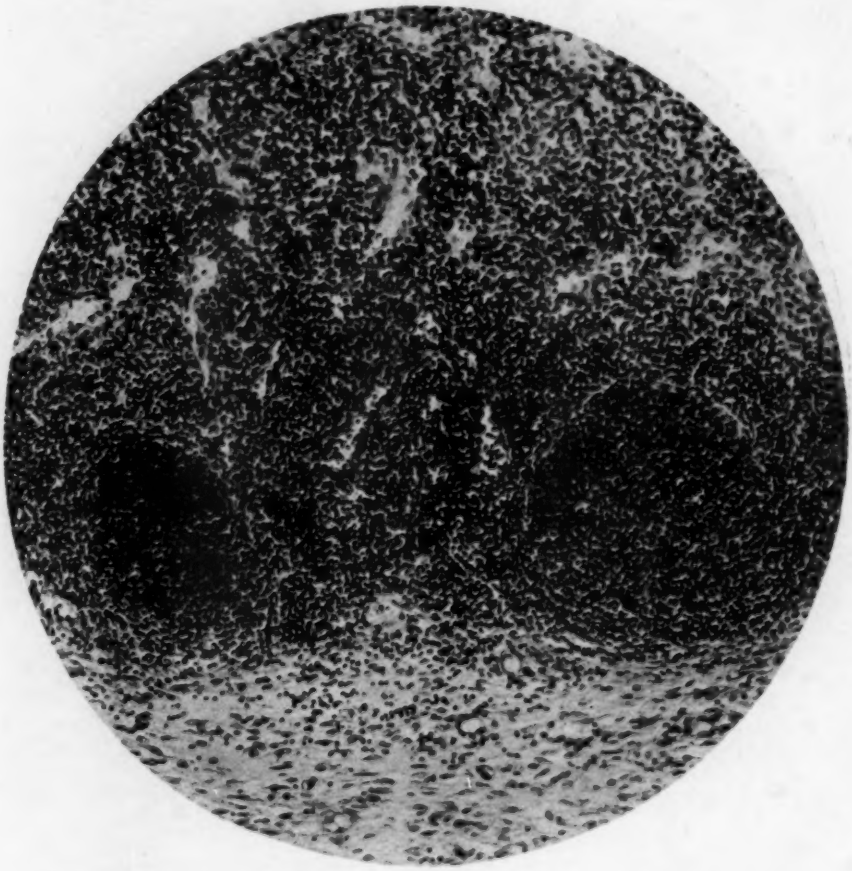

Fig. 6 (eight days).—Regenerated transplant with beginning formation of germinal centers.

lymphocytes were abundant and obscured the underlying reticulum. Active mitosis was observed throughout the transplant. The surrounding sinuses were filled with small lymphocytes.

Nine Day.—Well developed large transplant areas showed completely regenerated reticulum closely packed with small lymphocytes. Beginning formation of germinal centers such as are found in normal lymph nodes was observed.

Ten and Thirteen Days.—Fully regenerated large transplant areas showing a fully regenerated reticulum closely packed with small lymphocytes were present. Active mitosis was seen throughout the transplant.

Fourteen and Sixteen Days.—Sections showed fully regenerated, actively growing lymph node transplants with germinal centers. The transplant resembled a normal lymph node in all its essential features.

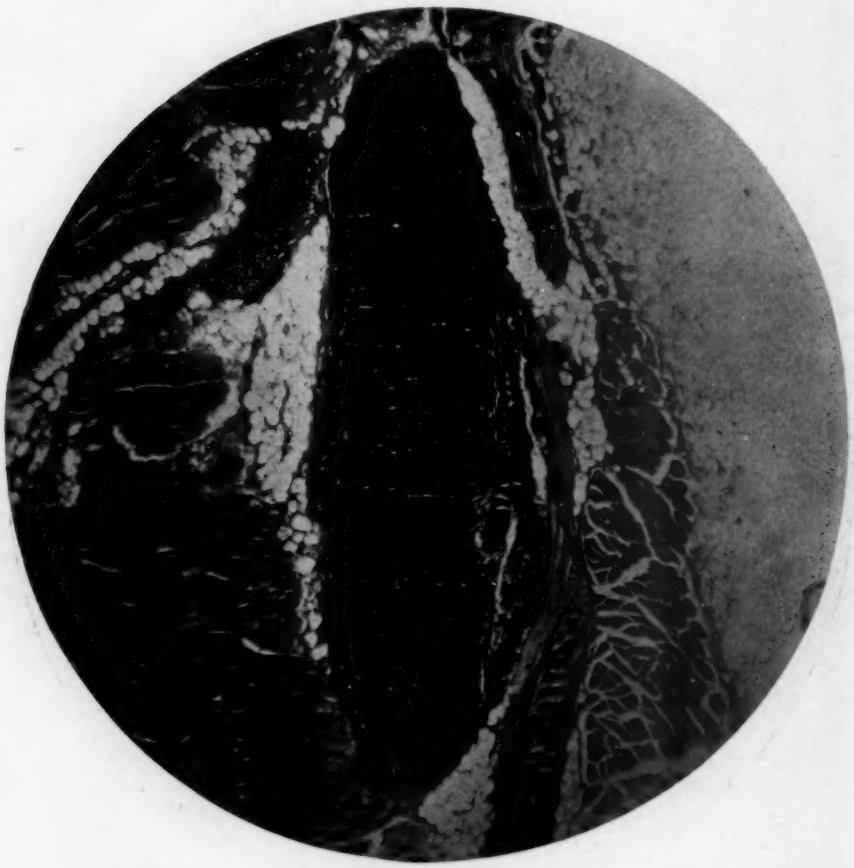

Fig. 7 (fourteen days).—Fully regenerated, actively growing, lymph node transplant, resembling a normal lymph node in all its essential features.

COMMENT

Our work shows that autoplastic transplants of the lymph nodes of young rats undergo a series of changes, in general, analogous to those found in the thymus transplants, but with one or two striking specific differences. These general changes consist of degenerative phenomena which begin during the first twenty-four hours and are most pronounced

at the end of this period, and regenerative phenomena which commence during the second day and reach complete regeneration by the end of the first week. At the end of the first twenty-four hours, the lymph node transplants show almost complete destruction of both reticular and lymphocytic elements, except for a small zone of well preserved

Fig. 8 (eight day thymus).—Extensive regeneration of the reticulum with almost complete absence of the small thymic cell. Large giant cells of the foreign body type surround the central area of necrosis.

lymphocytes at the periphery, with invasion by polymorphonuclear leukocytes, rapid phagocytosis and marked congestion of the surrounding blood vessels. After forty-eight hours, there is striking evidence of proliferation of the reticular cells from the outer zones, with extension of these elements in finger-like processes toward the center of the transplant. In the outer zone of regenerated reticulum, many newly

formed lymphocytes are seen. During the third day, mitotic figures are numerous. Small lymphocytes which are present as early as after twenty-four hours increase in the outer zone of the transplant. Transitional forms between fully developed lymphocytes and large oval reticular cells can be distinguished. During the following days, regeneration of both lymphocytes and reticular elements continues, and the small focus of degeneration which is still present in the center of the plant becomes progressively smaller. About the sixth day, giant cells appear about the focus of necrosis within the center of the plant. These giant cells appear to be formed by the fusion of reticular cells and must be considered as a foreign body giant cell reaction of the reticular elements to the focus of necrosis.

By the eighth day, regeneration of the node is almost complete. Masses of lymphocytes obscure the underlying reticulum, and in places have formed spherical accumulations resembling the follicles of the normal gland, with beginning formation of germinal centers.

For purposes of comparison, pieces of thymus of approximately the same size were transplanted into the abdominal wall of young rats, the technic described in a previous communication [9] being used. It was found in these transplants that about the seventh or eighth day, at the time when a marked proliferation of the reticulum is present, giant cells such as those described in the lymph node transplants appeared about the central area of necrosis. Transplants of thyroid tissue were inserted into the abdominal muscles of young rats in order to compare the regeneration with that of the thymus and the lymph node. In the thyroid gland, although a central area of necrosis occurred, as in the thymus and lymph node, there was not any giant cell reaction. This reaction is probably dependent on the relatively large quantity of reticular cells present in the thymus and lymph node tissues. Similar studies by Manley and Marine on transplants of the thyroid and spleen of the rabbit showed, likewise, an absence of giant cell reaction about the central area of necrosis, in the regeneration of their transplants.

In comparing the regeneration of the thymus to that of the lymph node, it is noted that: 1. Lymph node transplants regenerate more rapidly than thymus transplants of approximately the same size. In thymus transplants, all lymphocytic cells appear to undergo necrosis. 2. In the regeneration of the thymus, the entire transplant is completely replaced by reticulum before any small round cells appear. When round cells appear, they occur in scattered islands throughout. In the lymph node, however, lymphocytes are always present in the peripheral zone, and the lymphocyte and reticulum regeneration parallel each other. 3. In both the thymus and the lymph node, the reticulum arising from surviving reticular elements extends in finger-like projections from the periphery of the transplant. 4. In the thymus and the lymph node, the

small cell appears to arise from the reticular cells; transitional cells are distinguishable. 5. In both types of transplants, giant cells appear by fusion of reticular cells about the central area of necrosis in the course of the regeneration of the transplants.

SUMMARY

Autoplastic transplants of inguinal lymph nodes of young rats were studied at stated intervals. Comparative studies with thymus transplants were made, and the following results were obtained:

1. Over 95 per cent of the inguinal lymph nodes of young rats regenerate readily when inserted into the muscles of the abdominal wall.

2. Destructive changes occur during the first twenty-four hours when regenerative changes set in.

3. Regeneration commences with the reticulum which rapidly extends over the entire plant.

4. The regeneration is usually completed by the eighth day, when germinal centers begin to appear.

5. The lymphocytes arise from the reticular epithelium in the regeneration of the transplant.

6. In the development of the thymus transplant, the entire transplant is almost completely replaced by reticulum before any small cells appear. In the lymph node, however, the lymphocyte appears simultaneously with the regeneration of the reticulum and throughout it develops parallel with the reticulum.

7. A giant cell reaction of the reticular elements about the central focus of necrosis is noted in the lymph node and the thymus transplants. This giant cell reaction is not found in transplants of the thyroid and the spleen.

DOUBLE AORTIC ARCH *

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OMAHA

A survey of the literature dealing with anomalous conditions of the great vessels reveals only a few cases in which there is a persistence of both fourth brachial arches to form a double aortic arch. The following case is presented.

REPORT OF CASE

History.—An infant girl, aged 6 months, was admitted to the University Hospital on Nov. 16, 1927, because of a peculiar wheezing respiration, unusual cough and a beginning loss of weight. The baby had been delivered normally on May 6, 1927, weighing 9 pounds, 8 ounces (4.2 Kg.). Some cyanosis had been observed immediately after birth, and a peculiar wheeze was noted. The cyanosis cleared up promptly, and the wheeze was not again noted until the latter part of June and the early part of July. The patient was first seen in the outpatient department on July 21, at which time she weighed 13 pounds, 3 ounces (6 Kg.), and was 25 inches (63.5 cm.) tall. A roentgenogram made of the thorax on this date showed a slight widening of the shadow of the upper mediastinum, and, in view of the clinical history, a presumptive diagnosis of residual thymic enlargement was made. One radiation was given on that day. No further observations were made until the day of admission to the hospital, but the mother stated that the baby seemed to be better following the treatment until about September 1, at which time she again developed the peculiar wheeze and cough. At about this same time, the baby began to lose in weight and did not keep up its former activity.

Examination and Course.—On admission to the hospital, the baby weighed 12 pounds, 14 ounces (5.8 Kg.); the skin had a dusky, sallow hue; abnormalities were not noted in the examination of the cardiac area. Coarse, gurgling râles were heard all over the chest during inspiration, and a few minor inconstant changes were noted in the conduction of voice and breath sounds. The outstanding feature, besides the general appearance of the child which was that of severe illness, was the cough. It could be compared to the bark of a small dog, a series of short, sharp, staccato sounds, about six to eight in number, which occurred at rather frequent intervals and seemed to be initiated by any exertion. Examination of the upper respiratory tract did not disclose any point of obstruction. Urinalysis and examinations of the blood were not of diagnostic significance; the blood calcium was 12.4 mg. per hundred cubic centimeters. The observations in the physical examination may be summarized as: an undernourished child with a chronic, peculiar, staccato cough, wheezing respiration and coarse gurgling râles on inspiration.

During the stay in the hospital, the condition became steadily worse. Further roentgenographic studies of the thorax did not verify an enlargement of the thymus at this time; but a "rather unusual contour" of the upper portion of the heart shadow was reported, with an obscure interpretation. Bronchoscopic examinations were made on two occasions. On November 26, the instrument was passed with considerable difficulty and became lodged below the larynx. It was

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removed only after some maneuvering and laceration of the soft parts. On December 1, the examination was repeated with a smaller instrument, and a normal relationship of the larynx, without any apparent constriction as far down as the bifurcation of the trachea, was reported. About December 7, the baby's temperature, pulse rate and respiration curves began to rise, presenting the picture of infection. The cough became worse and was accompanied by spells of cyanosis. The number of stools increased to from six to eight a day and they had a foul, clinging, putrefactive odor. At about this time it was noted that the baby slept with its mouth open and its head drawn back. Râles of a different type from those heard previously now appeared over the posterior portions of the chest. Cyanosis and difficulty in respiration increased; the infant had an increased tendency to regurgitate its food. On December 26, the baby expired after a spell of choking and coughing.

Necropsy.—The body was undernourished but well developed and weighed 4,540 Gm. There were no external markings or deformities. The peritoneal cavity contained a normal amount of fluid, and the relationship of the abdominal viscera was normal. The entire gastro-intestinal tract was distended with gas; it was opened and examined from the lower third of the esophagus to the ampulla of the rectum. Within the stomach and small intestine, changes were not noted. In the large bowel, however, the mucosa was studded with many small ulcers varying from 1 to 10 mm. in diameter. Surrounding these ulcers there was little tissue reaction of an inflammatory nature. Microscopically, the ulcers consisted of small erosions of the mucosa with the underlying tissues densely infiltrated with lymphocytes. These areas were not associated with the lymphoid follicles.

The right lung was estimated to weigh more than twice the normal. Practically all of the lower lobe was airless; it was brownish red and felt nodular. These nodules could scarcely be seen on the sectioned surface, but were readily palpated. They did not give the impression of tubercles and acid-fast stains did not reveal any tubercle bacilli; however, a number of elongated cocci were present. A small amount of inflammatory exudate was observed on the sectioned surface. The left lung was similar to the right in appearance save for an additional anterior emphysema. Microscopically, the bronchi were seen to be filled with purulent exudate. The alveoli were partially collapsed and filled with endothelial cells and leukocytes, most of the latter being polymorphonuclears. A few areas of dense polymorphonuclear infiltration were seen which simulated early abscesses.

The heart was normal in size and position; the valves were competent to close the orifices. Neither the foramen ovale nor the interventricular foramen was patent. The great vessels, however, showed an unusual arrangement. The aorta left the left ventricle in the usual manner, passing up, forward and to the right. About 2.3 cm. beyond the point of its emergence, it divided into a right and a left branch which passed to either side of the trachea and esophagus to reunite posteriorly and form the descending aorta. The ascending aorta was 10 mm. in diameter, the right branch 8 mm. and the left branch 7 mm. About 3 mm. beyond the bifurcation, each branch gave off the respective common carotid artery. The left branch then gave off in rapid succession the left vertebral and the left subclavian arteries. These three vessels were given off within a space of 5 mm. Opposite the left subclavian artery, from the under surface of the left branch, the ductus arteriosus passed to join the pulmonary aorta. The ductus was 3 mm. in diameter and 9 mm. long and was patent throughout. This left branch of the aorta then passed posteriorly to join the right branch. The right subclavian artery arose from the right branch of the aorta, about 1 mm. posterior to the

right common carotid artery. The right branch then joined with the left branch on the right side of the vertebral column and passed to the lower portion of the thorax before crossing to its usual location.

The trachea and esophagus were thus entirely surrounded by an arterial ring the inner measurements of which were: anteroposterior, 12 mm., and transverse, 8 mm. The trachea above the ring measured 10.5 mm. in diameter and was constricted by the ring to a diameter of 7.5 mm. The lumen of the trachea above the stricture was 6.5 mm. in diameter, and at the point of constriction it was narrowed to an equilateral triangle which was estimated to be 4 mm. on a side.

The vagus nerves passed down laterally to the respective arches. The recurrent laryngeal nerve on the left side passed under the aortic arch and the ductus arteriosus to its normal course along the trachea. The recurrent laryngeal nerve on the right side unfortunately was cut in the dissection and not identified.

Microscopic studies of the heart, kidneys, spleen and liver showed only the usual changes of acute parenchymatous degeneration.

Pathologic Diagnosis.—Persistent fourth brachial arches with constriction of the esophagus and trachea; bronchopneumonia; ulcerative colitis.

Anomalous variations in the arrangement of the vessels of the upper mediastinum are not uncommon, but a total persistence of functioning double aortic arches is rare in the literature. Poynter [1] offers a classification of anomalies of the brachial arches and their branches, and in one group he places eighteen cases of "persistence of both fourth arches." A few of these cases are somewhat irregular in the arrangement of the branches given off by the arches, or in the course of patency of the arches themselves. The earliest case on record is that reported by Hommel in 1737, and the last one listed by Poynter is that of Gladstone and Wakeley in 1915. To this list two more cases may be added. One reported by Shaw [2] was observed in a man in the anatomic laboratories of the Rush Medical College. In general, it was similar to the case presented here, differing only in that the right arch was much larger than the left. The other case was reported by Buschendorff,[3] occurring in an infant, aged 1 month, who had a stridor similar to that described here; other features about the cases make them almost identical.

In addition, Brigham [4] reported another case from the anatomic laboratories of the University of Michigan Medical School, also occurring in an adult, in which, however, the posterior portion of the left arch was represented by a fibrous cord, the right arch carrying the systemic circulation. Four cases of anomalous arrangements of the aortic arches

1. Poynter, C. W. M.: Arterial Anomalies Pertaining to the Aortic Arches and the Branches Arising from Them, Lincoln, Neb., University Studies, 1916.

2. Shaw, D. L.: An Aorta with a Double Arch, J. A. M. A. **28**:538 (March 20) 1897.

3. Buschendorff, Carla: Beitrag zur Kenntnis der Persistenz eines Doppelten Aortenbogen und seine Klinische Bedeutung, Zentralbl. f. Herzkrankh. u. Gefäszkrankh. **9**:165 (Aug.) 1917.

4. Brigham, R. O.: Right Aortic Arch, Ohio State M. J. **18**:484 (July) 1922.

were reported by Wilhelm Ewald,[5] in none of which was there a total persistence of the entire left arch. One of these cases is, however, that of a 5 months old child in whom a persistent peculiar cough, a cyanosis which became more marked and was accompanied by dyspnea on swallowing and a definite tendency toward pulmonary infection were noted. In this patient an anomalous vessel arose from the descending aorta and passed toward the left subclavian artery but ended in a blind pocket before it joined with it; the balance of this remnant of the posterior portion of the left fourth brachial arch was represented by a fibrous cord joining the blind end of the vessel with the subclavian artery.

It is interesting to note that the anomaly was discovered in adults in five cases.[6] Those of Shaw, Brigham and Watson were discovered in anatomic laboratories, and nothing is known of the clinical histories. The case of Hamdi occurred in a Greek, aged 45, who, because of carcinoma of the lip, had undergone a radical operation for resection of the submaxillary and cervical glands, and had not evidenced any difficulty. Death occurred following a secondary plastic operation, and the anomaly was discovered at necropsy. The cases of Ewald and Buschendorff are, however, similar to the one here presented in that they occurred in children less than 7 months old and showed a similar clinical picture: stridor, persistent cough, cyanosis and a susceptibility to pulmonary infections.

Such anomalies are interesting from the standpoint of the persistence of fetal structures and of comparative anatomy. In birds, the right aortic arch is the one which normally persists. In reptiles, on the other hand, one finds a condition similar to that shown in this case—a persistence of both arches. This double existence of two aortic arches also occurs normally in the early embryonic life of the human being. A completely closed circulation first exists at about the second week of embryonic life and consists of the two umbilical veins, a single chamber heart and, on each side, an ascending aorta, an aortic arch and a descending aorta.[7] Later, the ascending aortas unite to form the truncus arteriosus, and the descending aortas unite to form the single descending aorta. The primitive aortic arches are represented in later embryonic development as the first brachial arches (fig. 1). Caudad to this first

5. Ewald, Wilhelm: Einige Fälle von Arcus Aortae dexter, Frankfurt. Ztschr. f. Path. **34**:87, 1926.

6. Shaw (footnote 2). Brigham (footnote 4). Watson, M.: Notes on a Case of Double Aortic Arch, J. Anat. & Physiol. **11**:229 (Jan.) 1877. Heller, A.: Doppelter Aortenbogen, München. med. Wchnschr. **51**:1666 (Sept.) 1904. Hamdi: Eine Seltene Aortenanomalie, Deutsche med. Wchnschr. **30**:1410, 1906.

7. Keibel and Mall: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2.

arch, five other arches appear, which connect the ascending and descending portions of the elongated arch, and form with it the six brachial arches. These six arches do not exist simultaneously, however, as the first two begin to disappear before the last two have become completely developed. (The existence of a fifth arch is in some dispute, since a definitely formed pharyngeal pouch cannot be demonstrated, and the vessels of the area are more of the nature of anastomoses than major vessels.[8])

The usual final disposition of the brachial arches is indicated diagramatically in figure 1. The first two arches disappear completely, the third persists, as the communication between the internal and

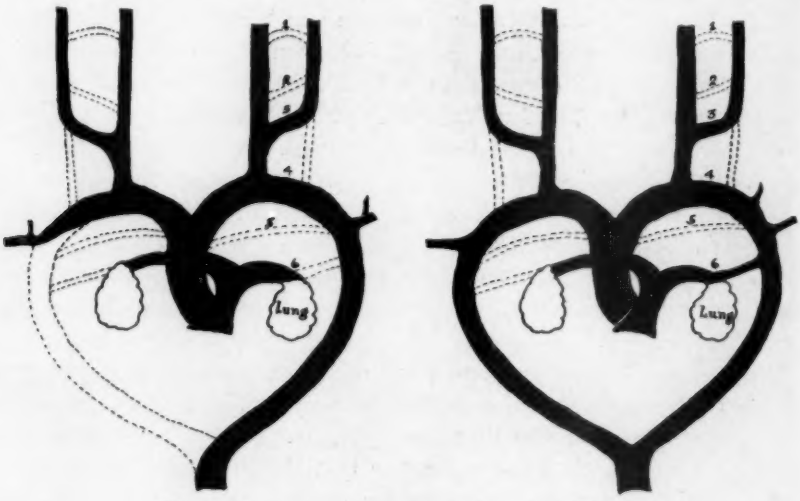

Figure 1 Figure 2

Fig. 1.—Normal disposition of the brachial arches.
Fig. 2.—Persistence of both fourth brachial arches and the ductus arteriosus.

external carotid arteries which are derived from ascending and descending arcs of the primitive aortic arch. That portion of the descending arc between the third and fourth arches also disappears. The fourth arch on the left side persists as the arch of the aorta, on the right side remaining only to the point at which the right subclavian artery originates. Beyond this point it too disappears. The fifth arches and the distal half of the right sixth arch are, likewise, not found in normally developed persons. The proximal portions of the sixth arches are represented by the pulmonary arteries, and the distal half of the left sixth by the ductus arteriosus of infants.

8. Ingalls, N. W.: Contrib. Embryol., Carneg. Inst., Washington, 1920, vol. 11.

Fig. 3.—Anterior view of specimen with the veins in situ, showing the bifurcation of the truncus arteriosus.

Fig. 4.—Antero-right lateral view with veins removed, showing the right aortic arch and branches.

Fig. 5.—Left side from above, showing the left aortic arch with the ductus arteriosus connecting the arch and the pulmonary aorta.

Fig. 6.—Posterior view, showing the union of the two arches to form the descending aorta.

The condition, as found in the case here reported, is shown by the photographs and diagramatically by figure 2. It will be noted that the arrangement is identical with that in figure 1, save for the connection between the right innominate artery and the descending aorta—the persistence of the right fourth brachial arch, and the origin of the left vertebral from the arch of the aorta instead of from the subclavian artery.

SUMMARY

A case is presented of a congenital anomaly in which there was a persistence of the posterior portion of the fourth brachial arch on the right side. This persistence resulted in the formation of an arterial ring which completely surrounded the trachea and esophagus, causing a decrease in the size of the lumen of these structures. The constriction of the trachea thus produced resulted in a marked stridor on forced expiration, and cyanosis whenever an increased demand for aeration was present. The compression of the esophagus resulted in some regurgitation of food and difficulty in swallowing. The factor which determines the disappearance of embryonic structures is still unknown, but whatever that factor may be, it is suggested that in this instance it was still functioning to some extent, since the arterial ring did not grow proportionately to the esophagus and trachea. Thus, in this case, the anomaly produced symptoms almost from the time of birth, whereas in other cases similar anomalies were found, quite by accident, in mature adults, who had led apparently normal lives.

CHICKEN-BONE PERFORATION OF THE ESOPHAGUS WITH BACTERIAL EROSION OF A LEFT BRONCHIAL ARTERY*

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Trauma of the esophagus which causes a laceration sufficiently deep to penetrate at once the large arteries of the thorax, or which by initiating an infection of tissue eventually opens a channel into the lumens of these vessels, has been reported from time to time. Because of the protection offered by its deepseated position, violence from the outside causing a rupture of the esophagus into the vessels mentioned is rare. The damage, then, which results in such perforations usually occurs from the inside of the esophagus and, except in all instances in which it is secondary to some disease such as carcinoma or to mechanical laceration in surgical manipulation, as in passing an instrument, is caused by the swallowing of some firm, rough or sharp object. It is commonly designated as "fish bone" or "chicken bone" injury.

We will describe such a laceration of the esophagus which initiated a bacterial infection of a tracheobronchial lymph gland and eventually led to the erosion of a left bronchial artery and fatal hemorrhage into the esophagus. A careful review of reports fails to disclose an instance in which a bronchial artery is involved in such a lesion. Poulet,[1] in 1880, collected thirty-three reports of perforations of the esophagus and blood vessels caused by some foreign body. In only two cases was the perforation caused directly by swallowing of the foreign body. All the others were caused by bacterial erosion of the blood vessel wall. Poulet grouped them according to the blood vessels involved as follows:

Aorta	17
Carotid artery,	
left	3
right	1
Superior vena cava	2
Inferior thyroid artery	1
Right coronary vein (small coronary vein)	1
Hemiazygos (demiazygos) vein	1
Right subclavian vein (abnormal)	1
Esophageal artery	1
Pulmonary artery	1
Unknown arteries (no autopsies)	4

* From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Poulet, A.: Foreign Bodies in Surgery, New York, William Wood & Co., 1880, vol. 1, p. 92.

Among the foreign bodies included are fish bones, a needle, a coin and false teeth.

Paul Krause [2] reported the case of a sailor, aged 22, who entered a hospital with the diagnosis of bronchial catarrh. While in the hospital, he vomited blood several times and then died. There were two ulcers of the esophagus, both of which had perforated it, and one extended into the arch of the aorta. The laceration in the arch of the aorta was about 5 mm. in diameter, and a fragment of bone was found in the infected tissues around the esophagus. Krause also reviewed the literature but since his inaugural dissertation is somewhat inaccessible the reports between 1877 and 1897 are here included.

Aschenborn [3] described the symptoms of a boy, aged 16, who swallowed a hard piece of bread and shortly afterward had severe pains in the region of the esophagus and the epigastrium. His fever was high and the condition was diagnosed as mediastinitis. Following several severe attacks of hematemesis he died. A long tear was found in the esophagus four fingerbreadths above the cardiac orifice of the stomach. Lying across the esophagus, at the level of the tear, was a threaded needle with its point projecting backward into the descending portion of the thoracic aorta.

Stetter [4] observed a sailor, aged 26, who swallowed a fish bone. An attempt was made to force the bone into the stomach. On the fifteenth day he had a violent hemorrhage from the mouth and died. The bone was found in the esophagus at the level of the bifurcation of the trachea. An ulcer of the esophagus had eroded the aorta, making an opening 1.5 mm. in diameter into the thoracic portion of the vessel, 2.5 cm. below the origin of the left subclavian artery.

Barkow's [5] patient, a boy, aged 15, swallowed a fish bone. A few days later he had severe hematemesis thought to be due to the perforation of a large gastric artery, and, accordingly, the right gastro-epiploic artery was ligated. Repeated attacks of hematemesis occurred, and he died five weeks after the accident. Although the fish bone was not found during the postmortem examination, there was a hole in the middle third of the esophagus and in the descending portion of the thoracic aorta.

Oliver [6] observed a woman, aged 40, who died from a violent hematemesis ten days after swallowing a fish bone. Three ulcers of the esophagus, one of them communicating with the thoracic portion of the aorta, were demonstrated in the postmortem examination:

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2. Krause, Paul: Inaug. Diss., Kiel, 1897.
3. Aschenborn: Berl. klin. Wchnschr. **14**:725, 1877.
4. Stetter: Langenbeck's Arch. f. klin. Chir. **22**:959, 1878.
5. Barkow, W. F. G.: Inaug. Diss., Kiel, 1895.
6. Oliver: Brit. M. J. **1**:954, 1909.

Rudiger's [7] patient, a woman, aged 56, swallowed a chicken bone. She died during a severe attack of hematemesis. A piece of bone was found piercing the esophagus and the aorta.

Turner [8] reported four patients in his own care. One, a child, aged 4 years, had swallowed a coin two years previously. A short time after this patient came to his attention, a large quantity of blood was vomited and death occurred. The coin was found in the esophagus opposite the left bronchus. The esophagus was ulcerated, and an infection had eroded the vessel just beyond the origin of the left subclavian artery. The second patient, a man, aged 54, swallowed a fish bone and died five days later. The bone was demonstrated projecting into the aorta. The third patient, a man, aged 40, died seven days after eating rabbit meat. A perforation of the esophagus and the aorta was demonstrated. The fourth, a man, aged 22, died on his way to the hospital. A bone was found perforating the esophagus and the aorta.

Taylor's [9] patient five days prior to entering the hospital swallowed a fish bone. On the day of admission to the hospital, she had two severe attacks of hematemesis; on the following day, she had two more attacks, and died. The fish bone was found projecing through the wall of the esophagus and there was a ragged wound in the aorta at the obliterated end of the ductus arteriosus.

Chiari [10] reported two cases. A woman, aged 28, died after repeated attacks of hematemesis thought to be due to pulmonary tuberculosis. Two ulcers of the esophagus were found during the postmortem examination. One of the ulcers had eroded the wall of the esophagus and led into tissues infiltrated with an exudate. This lesion further communicated with the thoracic portion of the aorta at the level of the fourth intercostal arteries by means of an opening in the aortic wall 3 mm. wide. A broken safety pin and a bent hairpin were found in the ileum. The second patient, a man, aged 47, swallowed a bone. Several attempts were made to pass an esophageal sound, and each time blood was returned. Six days later, an attempt to pass a sound was followed by severe hematemesis and death. A wound of the esophagus at the level of the incisura interarytaenoidea was found during the postmortem examination. The wound communicated with the aorta 1.5 cm. below the origin of the left subclavian artery.

Christopherson's [11] patient entered the hospital because of "something lodged in the throat." On the eighth day he vomited a large quantity of blood; the next day he died following another emesis of

7. Rudiger, R.: Wien. klin. Wchnschr. **22**:1066, 1909.
8. Turner: Lancet **178**:1335, 1910.
9. Taylor, C. J.: Brit. M. J. **1**:1207, 1913.
10. Chiari, H.: Berl. klin. Wchnschr. **51**:7, 1914.
11. Christopherson, J. B.: Lancet **1**:369, 1917.

a large quantity of blood. An ulcer of the esophagus was found adherent to the descending portion of the thoracic aorta in the vicinity of the bifurcation of the trachea. The ulcer had also eroded the wall of the aorta. Christopherson considered the probability of the esophageal ulcer being due to typhoid fever which the patient had had six years before.

Beal [12] reported the case of a woman, aged 60, who was found lying in a pool of blood. During the succeeding twenty-four hours she vomited bright red blood but did not present symptoms suggesting that it came from the lungs. She complained of severe pain in the precordial region that radiated down the left arm. She died after several attacks of hematemesis. A mass the size of a fist was demonstrated just above the base of the heart in the postmortem examination. In the wall of the esophagus opposite the arch of the aorta was a small irregular hole one fourth inch (6 mm.) in diameter. This hole was filled with a blood clot continuous with a large blood clot in the esophagus. The opening led into the mass in the mediastinum. In the arch of the aorta was a small opening one eighth inch (3 mm.) in diameter, and one and one half inches (3.75 cm.) to the left of the great vessels of the neck. This opening led into the same infected tissue as did the hole in the esophagus.

Seiffert [13] observed a woman, aged 48, who had swallowed a small bone; an attempt had been made to force it into the stomach. More than a week later she died with an acute anemia. A focal purulent mediastinitis and a perforation of the esophagus and the descending portion of the thoracic aorta at the level of the origin of an intercostal artery were found at autopsy.

Cramer's [14] patient, a man, aged 57, swallowed a bone and some time later died of a severe anemia. A perforation of the esophagus and the aorta was demonstrated after death.

Doria [15] made a postmortem examination on the body of a woman, about 30 years old, whose clothes were spotted with blood that flowed from the mouth, the nostrils and the anus. The stomach was distended with a huge blood clot. There was a perforation of the posterolateral wall of the arch of the aorta toward the esophagus. The opening was about 3 mm. in diameter, was round and had regular edges. There was not any inflammation around the opening. At the corresponding portion of the esophagus was a perforation of its wall, and partly resting in it was a triangular fragment of bone 2.5 cm. long with two

12. Beal, N. H.: Brit. J. Surg. **5**:512, 1918.
13. Seiffert, A.: Berl. klin. Wchnschr. **56**:299, 1919.
14. Cramer: Berl. klin. Wchnschr. **57**:1048, 1920.
15. Doria, J. R. da C.: Brazil-med. **39**:161, 1925.

sharp edges. It was evident from the esophageal ulceration that the bone had been there for a few days. The family reported that the woman had not felt well for several days, and two days before death a physician was summoned because of blood-stained sputum and vomitus.

Bostanier [16] observed a patient whose disease was diagnosed as a defect of the heart and a lesion of the brain. There was found, after death, besides multiple hematogenous abscesses, a fish bone perforating the left atrium of the heart. The bone probably was swallowed and perforated the esophagus and the pericardial sac before perforating the heart. The pericardial sac was empty, and death was due to septicemia.

Massa's [17] patient, a man, aged 26, swallowed a piece of bone which caused dysphagia and pain. A sound was passed down the esophagus and this treatment was followed by the vomiting of blood at intervals. A severe anemia resulted, and while he was being transferred to the hospital he vomited an enormous clot of blood and the bone. After a few days in the hospital his general condition improved and the hemorrhage stopped. On the tenth day, contrary to orders, he ate solid food; this again initiated the hemorrhages, and he died on the fourteenth day. A mass of granulation tissue about the size of a pea was found in the lining of the anterior wall of the esophagus at the level where the arch of the aorta passed into the descending portion. In the center of the granulation tissue was an erosion of the esophagus, and a sound passed through this opening entered the lumen of the aorta through the mouth of a posterior mediastinal artery. The tract communicating between the esophagus and the aorta extended from below upward.

Schlemann [18] reported several instances of foreign bodies in the esophagus which resulted in erosion of the esophageal wall and the wall of the common carotid arteries and the internal jugular veins.

REPORT OF CASE

A woman, aged 47, was admitted to St. Luke's Hospital on a stretcher because of hematemesis, syncope and pain in the epigastrium and under the sternum, all of which had been present for several days. The epigastric distress was practically constant and radiated upward under the sternum and to the back. The blood vomited was dark red and in clots. She had not noticed black stools. There was a marked pallor of the mucous membranes of the mouth, and a marked tenderness at the xiphoid process and along the left costal margin. A few râles were heard at the base of each lung. The red cells of the blood numbered 2,400,000, and the leukocytes 24,000 per cubic millimeter, and the hemoglobin content was 55 per cent, the temperature 100 F., the pulse rate 88 and the respirations 20. During the night she had a severe hematemesis, became cyanotic

16. Bostanier: Virchows Arch. f. path. Anat. **226**:269, 1919.
17. Massa, G.: Policlinico (sez. chir.) **25**:305, 1918.
18. Schlemann: Arch. f. klin. Chir. **114**:269, 1920.

and dyspneic and died quickly, nine hours after entering the hospital. A provisional diagnosis of gastric hemorrhage due to carcinoma or a ruptured esophageal varix was made, but she was not in the hospital a sufficient time for satisfactory observation and study, nor was an adequate history obtained. Later, a friend stated that ten days before entering the hospital the woman had swallowed a chicken bone.

The essential details of the postmortem examination (Edwin F. Hirsch) were as follows:

Anatomic diagnosis: foreign body (chicken bone [?]) laceration of the wall of the esophagus; acute suppurative inflammation of the regional tracheobronchial lymph glands; thrombosis and erosion of a left bronchial artery; mural thrombus of the aorta at the orifice of an eroded left bronchial artery; blood clot of the esophagus; huge blood clot in the stomach; marked anemia; obturating thrombosis of a second left bronchial artery; edema and emphysema of the lungs; calcified fibrous nodule (healed tuberculosis [?]) of the right lung; marked scoliosis of the spine; deformity of the sternum and costal cartilages; hyperemia of the lining of the sigmoid portion of the colon; fatty changes of the lining of the aorta and of the common iliac arteries; right pyelo-ureteritis and cystitis-cystica; stricture of the right ureter; ptosis and hydronephrosis of the right kidney; retention cysts of the lining of the cervix uteri; subserous and intramural fibromyomas of the uterus; small cysts of the ovaries; partially ossified costal cartilages; long-since absent teeth (thirty-two); carbon pigmentation of the lungs and the tracheobronchial lymph glands; slight fibrous changes of the leaflets of the aortic and the tricuspid valves; superficial abrasions of the skin of the right arm (two); multiple pigmented moles of the skin of the front of the trunk; old vaccination scar of the skin of the left arm; striae albicantes of the skin of the abdomen; bilateral hallux valgus; left intersigmoid fossa; persistent valve of the coronary sinus; slight fenestration of the leaflets of the aortic and the pulmonic valves.

The aorta was 5 cm. in circumference in its thoracic portion. Opposite the origin of the left subclavian artery and 2.4 cm. distal to it was an old slightly puckered scar, 1.2 cm. in diameter, representing the old aortic opening of the ductus arteriosus. On the anterior wall of the aorta, on a level with this scar, was an opening, 2 mm. in diameter, with irregular and slightly everted edges on one side and smooth edges on the other side opening into a left bronchial artery from which protruded a dark brown mural thrombus 6 mm. long and 4 mm. wide and thick. On the same level and 2 mm. to the right of this opening was the mouth of a second bronchial artery, an elliptic transverse slit 3 by 2 mm. There were slightly fatty changes of the lining of the aorta, more marked in the abdominal portion, but not involving more than 10 per cent of the lining. There was bright red clotted blood in the esophagus, and on the posterior wall at the level of the bifurcation of the trachea and 8 mm. above the level of the thrombus in the aorta was a perforation of the mucosa. It was a diamond-shaped slit with its longest dimension 1.2 cm. directed longitudinally, and 3 mm. at its widest part. A probe passed into this led into a necrotic encapsulated mass of lymphoid tissue just below the bifurcation of the trachea, and then entered the aorta through the mouth of the first mentioned left bronchial artery along side of the thrombus.

The mass of tissue between the esophagus and the aorta was 8.4 cm. long, 3.2 cm. wide and 1.2 cm. thick. It was gray-black, soft and necrotic in the central three fourths, while along the periphery it was firm black tissue like a carbon pigmented lymph node with a fibrous capsule about 1 mm. thick. Along side of

this fibrous capsule was embedded a branch of the azygos (?) vein and in the black lymph gland tissue were small, fibrous, gray-white masses from 1 to 2 mm. in diameter. From the orifice of the left bronchial artery, partly occluded by a thrombus, extended a tubelike structure 2 mm. long and 3 mm. in diameter (a portion of the left bronchial artery) into the necrotic mass. The other left bronchial artery was entirely occluded by a thrombus; the mouth of this vessel was 1 mm. in diameter. The tear in the esophagus also opened into the necrotic mass. There was thus a direct connection between the openings in the esophagus and the aorta through the necrotic tissue.

The amount of fluid and clotted blood in the stomach recovered and weighed was 950 Gm. The lining of the stomach was covered with a thick, tenacious fluid stained with blood. When this was removed there was a gray, normally smooth, finely pitted surface in all parts. Ulcers and erosions were not found in the lining of the bowel; dark brown blood was present in the lumen. Tarry fecal material was present in the rectum.

Streptococcus hemolyticus and *Staphylococcus pyogenes albus* were isolated from the tracheobronchial lymph node.

In histologic preparations of the necrotic tracheobronchial lymph gland only a small remnant of lymphoid tissue was observed. The remainder was necrotic and was invaded extensively by masses of polynuclear leukocytes.

SUMMARY

An account is given of a traumatic laceration of the esophagus by a chicken bone (?); this injury initiated a bacterial infection of a tracheobronchial lymph gland which eventually led to an erosion of a left bronchial artery with fatal hemorrhage into the esophagus.

SPONTANEOUS RUPTURE OF THE SPLEEN FOLLOWING VENOUS THROMBOSIS IN CARCINOMA OF THE PANCREAS

REPORT OF A CASE *

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This case of spontaneous rupture of the spleen following venous thrombosis in carcinoma of the pancreas, is reported not only because of its rarity, but also because of the clearness with which the sequence of events leading to the rupture may be interpreted. The only case in literature that resembles it is recorded by Hengeller.[1] In his case, a Chinese, aged 40, who died apparently from carcinoma of the head of the pancreas with metastases to the liver, showed, at autopsy, a rupture of the spleen, evidently brought about by a distention of the spleen due to recent thrombosis of the portal vein. Malaria, which is found in the greater number of cases of rupture of the spleen, was manifested in this case in the presence of pigment and atypical parasites in the spleen. Hengeller believed that malaria played a part in his case. In the case reported here, on the contrary, there was not any such complication observed. The clinical history and the postmortem observations may be briefly given, as follows:

History.—Mrs. M. J. K., aged 48, entered Barnes Hospital, March 15, 1926, complaining of pain in the abdomen. The family and personal history did not reveal anything of importance. The present illness began two years before admission, the patient complaining of weakness. Seven months before admission, she began having pain in the left upper quadrant of the abdomen, rather mild in character, but occasionally becoming severe and radiating to the lower part of the abdomen and to the back. The pain did not have any relation to meals, and was usually worse at night. She had had constipation for two years; occasionally she was nauseated and vomited.

The physical examination did not reveal anything essential to the case, except for a slight tenderness over the entire abdomen, more marked to the left of the umbilicus. A questionable mass was palpated in the epigastrium. The liver was felt 3 cm. below the costal margin.

The laboratory observations were as follows: The red blood cells numbered 5,000,000; the white blood cells, 6,200; polymorphonuclear leukocytes, 62 per cent. The hemoglobin content of the blood was 91 per cent. The Wassermann reaction was negative. The blood pressure was: systolic, 100; diastolic, 68. The examination of the urine did not show anything noteworthy.

An exploratory laparotomy, performed March 27, 1926, revealed an inoperable carcinoma of the pancreas. The postoperative course was uneventful for twelve

* From the Department of Pathology, Washington University School of Medicine and Barnes Hospital.

1. Hengeller, O.: Kor.-Bl. f. Schweiz. Artzl. **26**:758, 1896.

days, except for slight pain in the left side on April 5. The patient received a dose of deep x-ray therapy, April 7. The night following this treatment, she vomited and showed all the symptoms of shock: her pulse became weak and its rate irregular, and her blood pressure dropped to 62 systolic and 0 diastolic. The pain in the left side of the upper part of the abdomen at this time was more marked and radiated to the left shoulder. Her condition grew worse until her death, April 9.

Autopsy.—The body, which was poorly nourished and fairly well developed, weighed 51 kilograms and measured 165 cm. When the peritoneum was opened, blood rushed out. The peritoneal cavity contained about 800 cc. of fresh blood. Fresh blood clots were seen covering the liver and the spleen. The spleen was large. As the clot over the latter was gently removed, a tear was found in the capsule of the organ. A large hard mass was palpated in the region of the head of the pancreas, next to the duodenum. Several small conglomerate, grayish, hard nodules were noted on the peritoneal surface of the mesentery. The pleural and pericardial cavities did not show any change worthy of note.

The heart, lungs, liver and genito-urinary organs did not reveal any changes, gross or microscopic.

The spleen weighed 820 Gm. It was large, firm and purplish. It measured 18 by 13 by 8 cm. On the upper surface of the innermost aspect of this organ there was visible an irregular, elliptically shaped tear, measuring about 8.5 cm. in length and 1.5 cm. where it was widest. Another tear was noted over one of the notches of the spleen, which might, however, have been produced artificially during the removal of the spleen. On section, the spleen appeared as a deep red mass in which the malpighian corpuscles could not be seen. The trabeculae were visible here and there as fine gray lines. A few healed tubercles were noted in the capsule.

Lying in the elbow of the duodenum there was a large hard infiltrating tumor, cystic in the center and occupying the inner half of the pancreas. The splenic vein, which was seen in the lower-most portion of the tumor, was dilated to from 6 to 8 times its usual diameter, and contained an organizing thrombus that extended in the lumen of the vessel until it reached the spleen. The branches of the splenic vein, the pancreatic branch of the splenic artery and the branches of the superior pancreaticoduodenal artery were thrombosed. The bile duct was not compressed.

Microscopic Examination.—The spleen showed a pronounced congestion of the sinuses, practically obliterating the pulp tissue. Small malpighian corpuscles were seen here and there. A few scattered strands of connective tissue indicated the remains of the trabeculae. The capsule was thin and somewhat frayed. The subcapsular sinuses were less congested than the others. The arteries were small, and only slightly hyalinized. Thrombi were not found in the sections of spleen in any of the vessels. The polymorphonuclear leukocytes were rather prominent.

Pancreas.—The parts of the pancreas not affected by the tumor showed acini that were rather small, but many of the acini and ducts were distended. There was an increase in fibrous tissue in the interlobular and interacinous spaces. Some polymorphonuclear leukocytes were seen in the ducts. The tumor tissue consisted of thin strands of polygonal cells varying somewhat in shape and size, the nuclei especially showing marked variations. Many of these small strands were elongated, and some of them showed necrosis of the central cells, thus simulating an alveolar arrangement. Mitoses were not noted. The tissue was seen to invade vessels; a few cancer cells were found in the thrombosed splenic vein. The tumor tissue had a dense fibrous-tissue stroma. There was necrosis

of large areas of the tumor. Some of the tumor tissue was seen in the peripancreatic fat and in the peritoneal tissue of the mesentery.

Anatomic Diagnosis.—Spontaneous rupture of the spleen; hemoperitoneum; carcinoma of the head of the pancreas with metastases to the omentum; thrombosis of splenic vein and branches; thrombosis of pancreatic branch of the splenic artery and of branches of the superior pancreaticoduodenal artery; extreme congestion of the spleen; emaciation; chronic fibrous pleurisy.

The causal relationship between the enlargement of the spleen, the thrombosis of the vessels, and the carcinoma of the pancreas is clear. The invasion of the splenic vein by the tumor gave rise to coagulation of the blood, which was followed by subsequent complete obliteration and marked distension of the vein from the place of occlusion into the spleen. This condition itself was sufficient to bring about an acute congestion of the organ. The additional thrombosis of the neighboring veins, of the pancreatic branch of the splenic artery and of the branches of the superior pancreaticoduodenal artery decreased the possibility of some of the accumulated blood being shunted from the spleen. Thus, while blood could flow into the spleen, there was no outlet for it. The microscopic picture clearly revealed the extensive congestion of the blood sinuses of the spleen, of an intensity sufficient to lead to an almost complete replacement of the other elements of the organ.

An immediate cause of the rupture may have been a sudden muscular movement, taking place, for instance, during a change in position;[2] or it may have been a slight elevation of blood pressure. The possibility that the application of x-rays was an etiologic factor in the condition, is remote. Harbinson[3] irradiated the spleen directly with varying doses and did not find changes similar to those seen in this case. The application of x-ray therapy may have had, however, an indirect influence; namely, that of inducing muscular contractions by making it necessary to change the position of the patient. The spleen showed such extreme distension as a result of the congestion that a slight increase in abdominal pressure or in blood pressure was in all probability sufficient to cause a rupture.

SUMMARY

An unusual case of rupture of the spleen is reported. Thrombosis of the splenic vein secondary to carcinoma of the pancreas and thrombosis of the other veins of the spleen and of many of the arteries produced extreme congestion, which made rupture easily possible on slight exertion.

2. Playfair, G. R.: Edinburgh M. J. **2**:898, 1857. Stone, R. S.: Brit. M. J. **2**:469, 1878. Johannson, S.: Rev. de chir. **46**:58, 1912.

3. Harbinson, C. H.: Am. J. M. Sc. **167**:529, 1924.

Laboratory Methods and Technical Notes

THE KAHN TEST AS A HOSPITAL LABORATORY PROCEDURE*

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The use of the Kahn test in the serodiagnosis of syphilis has increased rapidly in the past few years. Likewise, reports from the many laboratories in which it has been tried have come to occupy a considerable place in the literature. The conflicting nature of these reports indicates the still somewhat disputed value of the test as a dependable diagnostic procedure. For this reason alone, we feel justified in adding this brief record, which represents our experience with the test as a routine laboratory procedure under hospital conditions.

The Kahn test was adopted in this hospital in order to determine its value and dependability under ordinary hospital laboratory conditions. Its value was determined by comparing the results of its use with those obtained by a standard Wassermann technic which has been employed here with satisfactory results for several years. In order to obtain unbiased results, the Kahn test was conducted by a person who had not had previous experience with it and who was unfamiliar with Wassermann technic. The Wassermann examinations were made by another person who did not have any knowledge of the Kahn test. The tests were run on identical samples of serum, these being the routine specimens from hospital, dispensary and prenatal clinic. The result of each test was reported independently of, and without knowledge of the outcome of, the other. Antigens used in each test were prepared by the workers performing the tests. In short, every effort was made to obtain accurate information as to the practical reliability of the Kahn test. This was accomplished, of course, by comparing it with the assumed dependability of the Wassermann test.

This study includes the serums, numbering 4,039, that were examined between Jan. 1, 1927, and Jan. 1, 1928. While this number is insignificant when compared with the hundreds of thousands of cases reported by military and state laboratories, it does represent the conditions of a large city hospital and also contains a series of 762 cases in which pregnancy existed.

* From the Otto Baer Fund for Clinical Research and the Philip and Emma Stein Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research.

RESULTS OF COMPARISONS

The results in brief were as follows:

		Percentage of Total
Total number of examinations	4,039	
Total number showing complete agreement between the results of the Kahn and Wassermann tests	3,694	91.4
Total number of disagreements, including smallest reported differences	345	8.6
Total number of disagreements in which there was a marked difference (more than ++)	93	2.30
Number of disagreements in which the Wassermann reaction was negative and the Kahn reaction slightly positive (+ or ++)	81	
Number of disagreements in which the Wassermann reaction was negative and the Kahn reaction strongly positive (+++ or ++++)	55	
	136	
Number of disagreements in which the Wassermann reaction was slightly positive and the Kahn reaction more strongly positive	47	
Number of disagreements in which the Kahn reaction was negative and the Wassermann reaction slightly positive (of these, ninty-four showed only + or ++ cholesterol with negative lipoid and syphilitic antigens)	138	
Number of disagreements in which the Kahn reaction was negative and the Wassermann reaction strongly positive	5	
	143	
Number of disagreements in which the Kahn reaction was slightly positive and the Wassermann reaction more strongly positive	6	

Analyzing the foregoing disagreements and comparing them with hospital and clinic records, so far as these were procurable, we obtained the following:

Of the 136 patients in whom the Wassermann reactions were negative and the Kahn reactions were positive, thirty-five, or 25.7 per cent, had clinically positive syphilis; fifty, or 36.7 per cent, did not have any clinical indications of the disease, and in fifty-one, or 37.5 per cent, information could not be obtained.

Of the 143 patients in whom the Kahn reactions were negative and the Wassermann reactions were positive, twenty-three, or 16 per cent, had clinically positive syphilis; fifty-nine, or 41.2 per cent, did not have any clinical indications of the disease, and in sixty-one, or 42.6 per cent, information could not be obtained.

Owing to the smallness of these groups and the incompleteness of the information, we merely present these figures without commenting on their significance.

Among the patients in whom there were disagreements between the Kahn and Wassermann readings, we have a series of forty cases known to be syphilitic who have been under treatment for varying lengths of time. Of these, thirteen, or 32.5 per cent, gave negative Wassermann and positive Kahn reactions; seven, or 17.5 per cent, gave negative Kahn and positive Wassermann reactions. Among sixteen in whom both tests were positive but varied markedly in degree of reaction, thirteen, or 32.5 per cent, gave Kahn readings which were stronger than the Wassermann readings; three, or 7.5 per cent, gave Wassermann readings which were stronger than the Kahn readings.

In treated patients, our experience agrees with that of most workers in indicating that the Kahn reaction is somewhat more delicate, and remains positive somewhat longer than the Wassermann reaction, as treatment progresses.

KAHN TEST IN PREGNANCY

The effect of pregnancy on the results obtained with the Kahn test is perhaps the most interesting part of this study. Thus far, this condition has been lightly treated in the literature, and we were able to find only one report in which the matter was specifically considered. Hinton,[1] in 1926, reported a small series of cases of pregnancy from which he concluded that the Kahn test is less reliable than the Wassermann test in pregnancy.

Our series includes 762 patients examined in the prenatal clinic. The results are as follows:

		Percentage of Total
Number of serums examined	762	
Number of complete agreements between Kahn and Wassermann reactions	725	95.2
Number of patients showing any disagreement between Kahn and Wassermann reactions	37	4.8

In considering the thirty-seven disagreements as closely as possible, we found historical and clinical records in all but seven of the patients. Of the thirty patients whose records we examined, ten gave negative Wassermann and positive Kahn reactions. In this group, only one history gave any significant indication of infection. This was an old case in which the patient had been treated, having previously had a ++++ Wassermann reaction. Sixteen patients had negative Kahn and positive Wassermann reactions. Of this number, none gave a definite history or physical evidence of syphilis. In only five were any possible indications recorded. Of these five, two had had two or three miscarriages, but several normal children. One patient was a primipara in whom the fetus was dead in utero at term. The baby of the fourth showed some scaling of the soles and palms, but not any other evidences of infection. The fifth case was one of septic abortion and the patient probably was not syphilitic.

Of three patients whose serums gave + Wasserman and ++++ Kahn reactions, two had positive histories of syphilis, while the remaining one did not present clinical evidence of the disease. One patient gave + Kahn reaction with a ++++ Wassermann reaction, and had also a history of existing infection.

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1. Hinton, W. A.: Kahn and Wassermann Reactions; Comparative Study, Boston M. & S. J. **194**:5 (Jan. 7) 1926.

COMMENT AND SUMMARY

Comparing the results in the pregnant patients with those in the whole number examined, we did not find any important difference in the results obtained when pregnancy existed. The percentage of disagreement between the Kahn and Wassermann reactions in these patients was essentially the same as that among the whole number of cases. The relative number of false reactions obtained by each test, as correlated with the available clinical evidence, does not differ markedly.

This series was too small to allow one to draw conclusions, and this we refrain from doing. However, our impression is that when pregnancy exists, the Kahn reaction is as reliable a criterion for the determination of the presence of syphilis as is the Wassermann reaction, if not actually more reliable. Moreover, in the whole series of examinations, disregarding the question of technic, we feel that the Kahn and Wassermann reactions are of about equal significance as indexes of syphilitic infection.

THE VALUE OF THE KAHN PRECIPITATION TEST AS APPLIED TO UMBILICAL CORD BLOOD*

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Most of the studies pertaining to the value of the Kahn precipitation test for syphilis have been made in comparison with one of the accepted complement-fixation tests. In this investigation the Kahn results were checked by the clinical observations only.

A determination of the reliability of the test in relation to certain minor points seemed desirable. The older Wassermann technics had a tendency to give false positive and negative reactions on blood from the umbilical cord and on blood drawn near the time of delivery; it was, therefore, deemed advisable to check this possible source of error in the Kahn test. Unfortunately, it has been possible to do so only with regard to false positive reactions. The material available consisted of blood from mother and child, secured in an institution which excluded syphilitic mothers. The series was, therefore, made up of blood from rigidly selected nonsyphilitic persons.

TECHNIC

Blood was drawn at the time of the admittance of the mother to the hospital; a sample of the blood from the umbilical cord was taken at delivery, and an additional sample of the blood of both mother and child was obtained about two weeks after delivery. The time of securing the antepartum specimen varied considerably, some being taken as early as the third month of gestation. The Kahn test was made within forty-eight hours on all specimens, the usual standard procedure being followed.

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* From the laboratories of the Methodist Hospital.

One hundred cases were thus studied in four tests, two on the mother, one on the cord blood and one on the 2 weeks old infant. In the entire series, only one nonsyphilitic positive reaction was obtained. A precipitate was not found in any of the tests made on the blood from the cords. From this evidence it may be concluded, then, so far as the danger of false positive reactions on the blood from the umbilical cord is concerned, that the Kahn precipitation test is reliable for such routine examinations.

Dr. Alma B. Richards furnished the material for this investigation.

General Review

THE ETIOLOGY OF ERYSIPELAS*

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EARLY HISTORY

The clinical history of erysipelas, when studied in combination with the pathologic and bacteriologic investigations expended on this disease, embraces almost every stage in the evolutionary progress of the art and science of medicine. Although the written history of this disease bridges the span of time from Hippocrates (about 430 B.C.) to the present moment, it was only sixty years ago that Vulpian (1868) accurately described the microscopic picture of the erysipelatous lesion and that Nepveu (1870) suggested in positive terms the parasitic nature of erysipelas.

Cumbersome obstacles were continually placed in the road of progress by a large host of pretentiously erudite physicians during the early and late middle ages. Instead of observing the erysipelatous lesion directly, these physicians were mainly concerned with prolonged discussions on the clinical character and possible complications of erysipelas. In addi-

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tion, Deprés, as late as 1862, lamented that "the proper erysipelatous lesions disappear in the cadaver," a fact which is untenable when the lesion is studied microscopically.

It is likely that Hippocrates first became acquainted with erysipelas in his discourses with physicians at the celebrated medical institution at Cnidos, for he often quoted their methods of healing and in that fashion preserved to us many monuments concerning that ancient state of the practice of medicine. In his "Epidemiorum," book III, Hippocrates [1] made the first written record of an epidemic of erysipelas, in words at once beautifully descriptive and adequately comprehensive, to the extent that the modern student of medicine may recognize therein the various stages observable in the idiopathic as well as the traumatic forms of the disease. Unfortunately, the "Father of Medicine" confused erysipelas with many acute inflammatory processes of the skin, subcutaneous tissues and internal organs. Certain etiologic factors were suggested, however, which merit quotation in their entirety, because of their ancient wisdom which is unsurpassed by modern writers on the same subject.

"Early in the spring," Hippocrates wrote, "at the same time as the cold weather occurred, many malignant cases of erysipelas were observed. Some of these were caused by known exciting factors, while others could not be readily explained. Many of the victims died and others suffered excruciating pains in the head. Many were attacked by the erysipelatous process over the entire body, when the initial lesion was a trivial trauma or slight abrasion. This was usually the case in patients about 60 years of age and when the inflammation was in the head, however slight the lack of hygiene might have been. Many of the patients undergoing treatment for severe inflammations would develop erysipelas which rapidly spread in all directions over the body surfaces. Many of the patients suffered with vesicles which terminated in suppuration. The serous substance secreted by these vesicles was not like ordinary pus; it was a different kind of suppuration presenting a copious and variable watery fluid. It was in the spring that the majority of cases of erysipelas occurred, although they continued throughout the summer and during the autumn."

It is of historical interest that Hipprocrates accounted for erysipelas as being due to atmospheric and telluric influences which favored the diffusion of poisonous substances in the bile and blood. These poisons, he believed, became fixed in parts of the skin and subsequently developed into erysipelatous lesions.

Celsus,[2] the celebrated physician under Augustus and Tiberius, also recognized erysipelas as a characteristic disease entity often known to

1. Hippocrates: Epidemiorum, book III, section III, chapters 3 and 4.
2. Celsus: Method. med., Basil, Almeloveen, 1748, book V, section 31.

cause serious complications in traumatic wounds, and yet at other times to arise idiopathically without any apparent external cause. In discussing the disease, he said:

"The affection which I called erysipelas, not only is superimposed upon a wound, but also occurs without a wound, and sometimes carries with it considerable danger, especially when it involves the entire face and scalp."

Galen [3] (130-201, A.D.) clearly differentiated between phlegmonous inflammation of the deeper tissues and erysipelas. He defined phlegmonous processes as inflammations more or less extensively invading the deeper tissues of the body, while erysipelas remained essentially in the skin and subcutaneous tissues. It is true, however, that in his later writings Galen confused erysipelas with a variety of infections in the skin, among which he haply recognized herpes as a distinctly peculiar form. Galen adhered to the teaching of Hippocrates that the disease was of biliary and sanguinary origin.

Like any tradition once firmly established by an acknowledged authority, more than cold facts are called on to displace it from the memory of man. It is, therefore, not surprising to find that the Greek physicians Oribasius,[4] Paulus [5] and Aetius,[6] the Arabian physicians Avicenne [7] and Ali Abbas,[8] the Salernian physicians Ruggero,[9] Rolando [10] and Guido de Chauliac,[11] and such writers as Heister [12] and Tissot [13] in the late eighteenth century declared themselves satisfied with the Hippocratic doctrine regarding the cause of erysipelas.

A slight modification of the teaching of Hippocrates appeared from the pen of a Danish physician named Lange,[14] who in 1520 elaborated on the biliary and sanguinary origin of erysipelas. He believed that capillary stasis brought about retention of the poisonous bile and blood in the affected parts of the skin. Ambroise Paré [15] and Fabrice d'Aquapen-

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3. Galen: Method. med., Kühn, 1748, vol. 10, book XIV, chapter 2, p. 949.
4. Oribasius: Synopsis, book VI, chapter 20; book VII, chapter 32.
5. Paulus: Basil, 1551, book IV, chapter 21, p. 341.
6. Aetius: Basil, Montano, 1535, book V, chapter 88, vol. 3, book XIV, chapter 60, p. 58.
7. Avicenne: Synopsis, book IV, chapters 13, 14 and 15; Canon, Venice, 1564, book IV, fen. 3, fract. 1, chapters 4 and 5.
8. Abbas, Ali: Pract., Lyons, 1523, book III, chapter 28.
9. Ruggiero: Chirurga, Salerno, Rienzi collection, vol. 2, book III, chapter 8, p. 472.
10. Rolando: Morb. med. ratio, book III, chapter 9.
11. De Chauliac, Guido: Chirurga, Lyons, 1572, tr. II, chapter 3.
12. Heister: Chirurgie, Nürnberg, 1770.
13. Tissot: Avis au Peuple, Paris, 1771, chapter 19, section 273.
14. Lange: Gaz. hebd. de méd., 1863, p. 30; Bermaerkninger om Grönlands Sygdomsforholde, Copenhagen, 1864, p. 37.
15. Paré: Oevres complete, Paris, Malgaigne, 1841, vol. 2, p. 27.

dente [16] (1531) accepted the thesis of Lange and corroborated it with elaborate commentaries and clinical observations.

It was only in the nature of events that erysipelas should also be subjected to sacerdotal embellishment and thus steeped in supernaturalism. This period gave rise to the legend that St. Anthony (1195-1231), whose eloquence was so great that fishes were reported to jump out of the water to hear him preach, could miraculously cure erysipelas and remove the spell of the "Evil Eye" which brought about the disease. Since that time erysipelas has been termed St. Anthony's Fire. It is, however, of more than passing interest that Paracelsus [17] (1491-1541), when a professor at the University of Basle, declared that erysipelas is caused by the devil and the revolt of angels.

Following a long period of belief in witchcraft and astrology, in which many innocent victims afflicted with erysipelas were persecuted and punished with death, the pendulum swung back to the Hippocratic doctrine. The most brilliant medical men of that period, such as Sydenham [18] (1624-89) in England, and Boerhaave [19] (1669-1738) in Holland, freely subscribed to the biliosanguinary origin of erysipelas, without contributing materially to a fuller knowledge of the disease. By this time the pathologic approach to rational and especially to preventive medicine was opening out.

ANATOMIC AND CLINICAL PERIOD

During the inspiring period of microscopic investigations inaugurated by Morgagni [20] (1682-1771), erysipelas was subjected to a series of interesting studies by Platner,[16] Sauvages,[21] Lorry,[16] Arnold [22] and Vogt,[23] and a few years later by Pinel.[16] By striving to connect the pathologic lesions with the symptoms and signs of the disease during life, these investigators made the first attempts to determine the actual localization of erysipelas by means of microscopic studies. Borsieri,[24] in 1734, believed that all the layers of the skin, the subcutaneous tissues, muscles

16. Quoted by Achalme: Considerations pathologeniques et anatomo-pathologiques sur l'erysipele, Thèse de Paris, 1892.

17. Paracelsus: De daemoniacis et obsessis, Berlin, Sudhof, 1894, vol. 2, p. 235.

18. Sydenham: The Whole Works of Thomas Sydenham, London, 1701, chapter 6, pp. 206-209.

19. Boerhaave: Academical Lectures on Theory of Physic, London, 1751.

20. Morgagni: De sedibus et causis morborum, Nona, book IV, epist. 59.

21. Sauvages, quoted by Ziemssen: Cyclopedia of Practice of Medicine, New York, 1875, vol. 2, p. 426.

22. Arnold: Dissertation, Vitab., 1802.

23. Vogt: Caussae ad frequentiorum erysipelatis reditum predisponentis exponuntur, Wittenberg, 1802.

24. Borsieri, quoted by Ziemssen: Cyclopedia of Practice of Medicine, New York, 1875, vol. 2, p. 426.

and blood vessels were involved in the erysipelatous lesion. Callisen,[25] in 1783, made the first accurate localization of the disease when he stated that "erysipelas is an inflammation which affects the surface layers of the skin, leaving the underlying tissues intact; the disease usually changes its surface position by direct extension." He further stated that "seldom or ever is one confronted with a suppurating process in true erysipelas, unless the disease entity changes, as it occasionally does into a phlegmonous process."

Rust,[26] in 1832, attempted to establish a differential diagnosis between erysipelas, phlegmons, purpura, erysipeloid and allied cutaneous lesions. His studies corroborated the observations of Callisen that erysipelas is strictly confined to the layers of the skin and subcutaneous tissues. Although he freely admitted the distinct rôle played by individual susceptibility in contracting erysipelas, he still defended the biliosanguinary theory as to the cause of the disease. The data which served as basis for his support of the biliosanguinary origin of the disease is rather meager, for he states that "emotional upsets, such as fright, anger and hate bring about erysipelas, since when these persons are made to vomit during their emotional upset, they bring forth acrid bile, which proves that the disease is closely linked up with certain biliary processes in the abdomen."

Following the advice of Bichat,[27] medical investigators were now looking beyond organs to tissues for the seat of disease. So far as the study of erysipelas was concerned, two schools of opinions dominated during the middle of the nineteenth century. One group held that erysipelas was a combination of phlebitis and inflammation of blood vessels and venous capillaries. This opinion was shared by Flandin,[28] Ribes,[29] Cruveilhier,[30] Bouillaud [31] and Beraud.[32] The other group held that erysipelas was an inflammation of the lymphatic vessels, and this belief was held by Blandin,[33] Velpeau [34] and Després.[35]

Copland [36] placed himself between these two extreme opinions, by suggesting that true erysipelas often becomes complicated by lymphangi-

25. Callisen: Einleitungssaetze in die Chirurgie, Frankfurt and Berlin, 1783.
26. Rust: Handbuch der Chirurgie, Berlin, 1832.
27. Bichat: Anatomie generale, Paris, 1801, vol. 4, p. 758.
28. Flandin: J. compl. du dict. sc. méd., Paris, 1831, vol. 41, p. 68.
29. Ribes: Mém. de la Soc. méd. d'emul., Paris, 1822, vol. 8, p. 622.
30. Cruveilhier: Traite d'anat. pathol., 1862, vol. 4, p. 252.
31. Bouillaud: Rev. méd. **2**:71 and 418, 1825; Gaz. d. hôp. **1**:265 and 271, 1839.
32. Beraud: L'experience, Paris, 1839.
33. Blandin: Lancette française **5**:434, 1831; Pathol. de Nelaton, 1857, p. 554.
34. Velpeau: Arch. gén. de méd. **13**:189, 1827.
35. Després: Traite de l'erysipele, Thèse de Paris, 1862; Gaz. méd. de Paris **17**:649, 1862.
36. Copland and Hutchison: Med. Chir. Tr., London **14**:213, 1828.

tis and phlebitis. Already, in 1837, Sanson [37] had suggested that two types of erysipelas existed, namely, a lymphatic inflammation and a venous inflammation. Gendrin [38] attempted to settle this prolonged dispute. He studied normal as well as erysipelatous skin by microscopic methods, and arrived at the conclusion that erysipelas involves only the layers of the corium and the immediately adjacent subcutaneous tissue, and that a proliferative inflammation of the lymphatics is in evidence within the erysipelatous lesion. Piorry,[39] in 1862, concurred in these results and subsequently named the clinical picture "septico-dermite," according to its anatomic distribution and pathologic involvement.

With the rapidly advancing science of anatomy and pathology and the advent of bacteriologic methods, erysipelas gradually emerged from the realm of speculative contention into a positive phase of objective demonstration and experimentation. During this period, the work of Vulpian,[40] which appeared in 1868, demonstrated beyond reasonable doubt that the edematous congestion of the skin and underlying tissues in the erysipelatous lesion is mainly due to the penetration into those tissues of large, finely granular leukocytes which uniformly permeate the tissues without any attempt at organization.

This important observation was confirmed the same year by Volkmann and Steudener,[41] who found masses of leukocytes in a state of finely granulated disintegration throughout the subcutaneous cellular tissue. In the upper layer of the cutis only the lymphatic vessels were thickly filled with the uniform granulated cells or were surrounded with large collections of them. These authors believed that a portion of the leukocytic elements was taken up by the lymphatics, although they noted that the majority rapidly perished, and that within a few days after resorption of the erysipelatous lesion no trace of the leukocytic elements was detected. These observations were corroborated by Liouville,[42] Cadiat [43] and Lordereau [44] in 1873.

Renaut,[45] in 1874, published a most comprehensive and original investigation on the microscopic changes of erysipelas, wherein he stated that

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37. Sanson: Presse méd. **1**:401, 1837.

38. Gendrin: J. gén. de méd., Paris **101**:185, 1827.

39. Piorry: Gaz. méd. de Paris **1**:12, 1833; Lancette française **1**:285, 1829; Gaz. d. hôp. **31**:321, 1858.

40. Vulpian: Arch. de physiol. norm. et path. **1**:314, 1868.

41. Volkmann and Steudener: Centralbl. f. d. med. Wissensch. **6**:561, 1868.

42. Liouville: Soc. de biol., 1872.

43. Cadiat: Bull. et mém. Soc. anat. de Paris **48**:834, 1873; ibid. **49**:770, 1874; J. de l'anat. et de la physiol. **10**:410, 1874.

44. Lordereau: Thèse de Paris, 1873.

45. Renaut: Compt. rend. Soc. de biol. **5**:136, 1873; L'etude anatomique de l'erysipele et des oedemes, Thèse de Paris, 1874; Progrès méd. **1**:221, 1873.

as a rule only the lymphatic vessels are involved in the disease processes and that definite changes are never observed in the blood vessels. After a careful study of vesicle formation, Renaut concluded that this anomaly is brought about by blockage of the lymphatics by excessive numbers of leukocytes. He likewise suggested that the erysipelatous process ends by resolution and that the leukocytic and lymphocytic elements finally disappear completely from the cutaneous and subcutaneous tissues. The occasional residual induration of the previously affected parts of the skin and subcutaneous tissue, Renaut ascribed to proliferation of embryonic cellular elements attempting to restore the tissues to normalcy.

Cornil and Ranvier,[46] in 1876, wholeheartedly supported Renaut's thesis. Although a large group of investigators have since busied themselves with the pathology of erysipelas, nothing new of exceptional merit was added to the previously discussed studies, which finally Achalme,[47] in 1892, reviewed in masterly fashion by combining all the available knowledge of his predecessors into a thesis on erysipelas.

The study of erysipelas next entered on its bacteriologic treatment, which was delayed considerably by the absence of adequate methods and means for the detection and cultivation of micro-organisms.

BACTERIOLOGIC PERIOD

Toward the end of the eighteenth century many investigators had the fortitude to challenge the time-worn Hippocratic doctrine of the biliosanguinary origin of erysipelas. In England, John Hunter [48] and Gregory [49] advocated the contagious nature of this disease. On the Continent, Lorry,[16] Piorry,[50] Velpeau,[51] Trousseau,[52] Lefort [16] and a large group of physicians wrote about the parasitic nature of erysipelas. From 1865 to 1869, the French investigators defended hypothetically the belief that the primary cause of this disease is a parasite which enters abrasions in the skin or mucous membranes and in those portals of entry initiates the symptoms and signs typical of erysipelas.

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46. Cornil and Ranvier: Manuel d'histol. pathol., Paris **1**:153, 1876.

47. Achalme: Considerations pathologeniques et anatomo-pathologiques sur l'erysipele, Thèse de Paris, 1892.

48. Hunter: The Works of John Hunter, London, Palmer, 1835, vol. 3, p. 313.

49. Gregory: Lectures on Fevers and Inflammations, Edinburgh, 1777.

50. Piorry: Lancette française **1**:285, 1829; Gaz. méd. de Paris, 1832, p. 281.

51. Velpeau: Lancette française **5**:105, 1831; J. de méd. et chir. pract. **12**:259 and 318, 1841; Arch. gén. de méd. **8**:129, 1835; Gaz. d hôp. **2**:435, 443, 521, 525 and 546, 1870.

52. Trousseau: J. de méd. de beau. **2**:1, 1844; Clinique européenne, 1859, p. 26; Lectures on Clinical Medicine, New Sydenham Society, London, 1868, vol. 2, p. 251.

Volkmann,[53] in 1869, gave his support to this belief and openly stated that "erysipelas is a wound-infection directly dependent upon the destructive activity of peculiar poisons produced by pathogenic bacteria."

Hueter,[54] in 1868, announced the discovery of "monas erupusculum," a bacterium isolated simultaneously from erysipelas lesions and the throats of patients with diphtheria. The author claimed that erysipelas and diphtheria uniformly were caused by this organism. Hueter's study is not convincing and still remains unconfirmed.

Nepveu,[55] in 1870, was the first investigator to describe micrococci in the erysipelatous lesions and the blood of patients with erysipelas. He described these organisms as "delicately oval-shaped, rapidly movable, and very variable in sizes." The exceptional presence of micrococci in the blood stream of patients with erysipelas and the inability of streptococci to display anything but Brownian movements in the hanging-drop preparation, somewhat invalidate the claim of Nepveu of having discovered the etiologic agent causing erysipelas.

Wilde,[56] in 1872, reported the interesting observation that "pus from wounds where the erysipelatous lesions start contains numerous micrococci." Orth,[57] in 1873, demonstrated "micrococci in chain-formation in the contents of the erysipelatous bullae." Displaying a remarkable ingenuity, Orth injected under the skin of a rabbit the contents of the erysipelatous bullae, in which were found numerous streptococci. Within twenty-four hours, an inflammatory process developed, entirely analogous with erysipelas in man. By application of the edematous fluid expressed from the subcutaneous tissue of the experimentally developed erysipelatous lesion to a second rabbit, the characteristic progressive inflammatory lesion of erysipelas was communicated to the latter animal. In the edematous cellular tissue as well as in the affected parts of the skin of the rabbit afflicted with erysipelas, Orth demonstrated the presence of streptococci. By these convincing experiments, Orth fulfilled the postulates laid down by Koch for the detection and demonstration of specific micro-organisms, except that he failed to isolate the streptococci in pure culture.

Pitoy,[58] in 1873, obtained similar results with fluid expressed from erysipelatous lesions and vesicles, but, unfortunately, neither of these investigators had the opportunity to cultivate these micro-organisms outside the human or animal organisms.

53. Volkmann: Berl. klin. Wchnschr. **33**:357, 1869; Pitha-Billroth, Berlin, 1869.

54. Hueter: Deutsche Ztschr. f. Chir. **1**:1, 1868; Grundriss der Chirurgie, Berlin, 1880.

55. Nepveu: Compt. rend. Soc. de biol. **22**:164, 1870.

56. Wilde: Med. Jahrb. **155**:104, 1872.

57. Orth: Arch. f. exper. Path. u. Pharmakol. **1**:81, 1873.

58. Pitoy: Thèse de Paris, 1873.

In 1874, Lukomsky [59] made the important discovery [60] that "the lymphatic vessels and lymph spaces in the skin at the margin of the erysipelatous lesion are filled with micrococci." Employing almost primitive methods, these investigators isolated similar micrococci from the kidneys and lungs of patients who died of erysipelas. The latter observations are not necessarily typical in any disease entity which terminates fatally. Nevertheless, these observations were corroborated by Letzerich,[61] in 1875, and Billroth and Ehrlich,[62] in 1880, who also reported micrococci were present in the liver and genito-urinary tract of patients who died of erysipelas.

Tillmanns,[63] in 1880, reported his inability to demonstrate micrococci in other organs except in erysipelatous lesions. Bouchard,[64] in 1880, confirmed this observation and illustrated the presence of diplococci and streptococci in the fluids expressed from erysipelatous bullae.

In spite of the accumulation of impressive literature substantiating the bacterial causation of erysipelas, it is difficult to understand how such eminent authorities and investigators as Lukomsky, Billroth, Ehrlich, Tillmanns, Wolff [65] and others should have discountenanced the *a priori* relationship of streptococci to erysipelas. On the contrary, these men advocated that the micrococci accidentally present in the erysipelatous lesions played the singular rôle of carrying poisonous, nonorganized substances to the inflamed areas. These poisonous substances were held to be the primary cause of erysipelas.

During this period a great many theories were promulgated and the etiology of erysipelas remained buried in confusion, although most of the essential pathologic and bacteriologic knowledge had already been disclosed to fix the disease as a specific entity. The final criterion for the actual determination of the cause was missing, largely because of inability to cultivate bacteria outside the human or animal body. This difficulty was first solved when Koch,[66] in 1880, introduced his technical methods which at once revolutionized medical thought and rapidly made bacteriology an exact science. Koch's matchless contribution to the physician's

59. Lukomsky: Virchows Arch. f. path. Anat. **60**:418, 1874.

60. This work was done with von Recklinghausen whose name does not appear in the title of the article.

61. Letzerich: Virchow-Hirsch Jahresbericht, 1875, p. 69.

62. Billroth and Ehrlich: Arch. f. klin. Chir., vol. 2, p. 460; vol. 4, p. 537; vol. 9, p. 139; vol. 20, p. 418.

63. Tillmanns: Deutsche Chir., 1880; Deutsche med. Wchnschr. **4**:224, 1878; Arch. f. klin. Chir. **23**:437, 1879; Erysipelas, Stuttgart, 1880.

64. Bouchard: Course de la pathologie generale, 1880; Maladies infectieuses, Paris, 1889.

65. Wolff: Virchows Arch. f. path. Anat. **81**:193, 1880; Berl. tierärtzl. Wchnschr. **6**:1, 1899.

66. Koch: Mitteilungen aus dem kaiserlichem Gesundheitsamte **1**:38, 1881.

armamentarium in his fight against infectious disease ushered in a new era which was usually fruitful in the history of medicine.

Aided by Koch's discovery of the solid nutrient medium, which made possible the artificial cultivation and isolation in pure culture of bacteria, Doleris,[67] in 1880, under the direction of Pasteur, gave the first accurate description of streptococci isolated in pure culture from erysipelatous lesions. Dupeyrat,[68] in 1881, repeated this work and succeeded in producing typical experimental erysipelas in rabbits, according to the method demonstrated by Orth in 1873.

Finally, it remained for Fehleisen,[69] in 1882, to discover beyond any reasonable doubt that *Streptococcus erysipelatis* is constantly present in the lymphatic vessels within the erysipelatous lesion, and that the organism can readily be cultivated in pure culture outside the human or animal body.

To obtain the streptococcus from erysipelas in human beings, Fehleisen excised small pieces of skin near the margin of the erysipelatous lesion. These pieces of skin were immediately placed in test tubes containing nutritive gelatin medium. The tube was kept for two hours at 40 C. in order to liquefy the gelatin and bring the medium into close contact with the pieces of skin. The tubes were next allowed to remain at room temperature for a few hours; then the contents were poured into sterile Petri dishes. These plates were kept at room temperature for several days until the streptococcic colonies became visible.

Having isolated *Streptococcus erysipelatis* in pure culture, Fehleisen proceeded to produce experimental erysipelas in nine rabbits with the cultures. In this he was highly successful, and he was able to reisolate the pure culture of the streptococcus from experimentally produced erysipelas.

Fehleisen remained dissatisfied with the experimental production of erysipelas in the rabbit. Displaying an almost inhuman scientific interest in the subject of the etiology of erysipelas, he attempted to repeat the experiments of what Hebra,[70] in the seventeenth century, and Ricord and Despres,[71] Busch,[72] Champouillon,[73] Zarubin,[74] von Knopff[75] and

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67. Doleris: Thèse de Paris, 1881; Compt. rend. Soc. de biol. **45**:1051, 1893.

68. Dupeyrat: Thèse de Paris, 1881.

69. Fehleisen: Deutsche med. Wchnschr. **8**:553, 1882; Die Aetiologie des Erysipels, Berlin, 1883; Deutsche Ztschr. f. Chir. **16**:391, 1882; Wien. med. Presse **23**:1329, 1882.

70. Hebra: Virchows Handbuch d. Pathol. u. Therap., 1872.

71. Ricord and Despres, quoted by Fehleisen (footnote 69, p. 20).

72. Busch: Verhandl. d. naturh. Ver. d. preuss. Rheinl. u. Westphal. **23**:28, 1866; ibid. **25**:330, 1868.

73. Champouillon: Rec. de mém. d. méd. mil., Paris **23**:330, 1869.

74. Zarubin: Ejened. klin. gaz., St. Petersburg **1**:521, 1881.

75. Von Knopff: Berl. klin. Wchnschr. **19**:290, 1882.

Wright,[76] in the nineteenth century; i.e., the inoculation of human beings with living micro-organisms contained in erysipelatous vesicle fluid, in the treatment of psychosis, neuralgia, acute rheumatic fever and malignant tumors. In this fashion, Fehleisen was permitted to reproduce erysipelas with pure cultures of *Streptococcus erysipelatis* in seven persons suffering with malignant growths. Six of the patients developed typical erysipelas which spread across the area involved by the malignant tumors. Following their convalescence, Fehleisen noted retrogression of the tumor in some of the patients. This practice must have fallen into disrepute because of unfortunate accidents, for little or nothing was written subsequently on the subject. Therapeutic benefits were reported by Esteves,[77] Rasch,[78] Collins,[79] Koch and Petruschky [80] and Whitehead.[81]

In this inspiringly dramatic search for scientific truth, several interesting and highly instructive features of erysipelas were brought to light by Fehleisen's experiments on human beings, namely, that the incubation period in erysipelas varies from fifteen to sixty-one hours, and that there is a temporary immunity to reinfection with *Streptococcus erysipelatis*. This latter conclusion was drawn from the incident that among the seven persons inoculated with living organisms, six developed typical erysipelas, while the seventh failed to react after two massive inoculations. Fehleisen learned that this patient had suffered recurrent attacks of erysipelas and had had his last attack only three months previously.

The many authors who have since written on the subject of erysipelas have largely reproduced the original results of predecessors and, in particular, those of Fehleisen. The most important confirmations of the specificity of *Streptococcus erysipelatis* came from Hajeck,[82] Denuce,[83] Verneuil,[84] Babes [85] and Metchnikoff.[86] These investigators produced experimental erysipelas in rabbits with pure cultures of the erysipelas streptococcus of Fehleisen. Many irregularities began to creep into the experimental production of erysipelas. Much of the confusion can readily be explained on the basis of a rapid loss of virulence of the streptococci cultured on artificial medium without occasional

76. Wright: Am. J. M. Sc. **4**:23, 1829.

77. Esteves: Ann. de Circ. med. argent., Buenos Aires **8**:84, 1885.

78. Rasch: Tidsskr. f. prakt. med., Christiania **7**:387, 1887.

79. Collins: Times & Reg. **27**:268, 1894.

80. Koch and Petruschky: Ztschr. f. Hyg. u. Infektionskrankh. **23**:477, 1896.

81. Whitehead: Brit. M. J. **1**:1238, 1907.

82. Hajeck: Berl. med. Wchnschr. **25**:320, 1888; Wien. med. Presse **27**:1563, 1590, 1623 and 1655, 1886.

83. Denuce: Thèse de Bordeaux, 1885.

84. Verneuil: Soc. de chir. **1**:190, 242, 254 and 269, 1872; Gaz. d. hôp. **4**:12, 1878.

85. Babes: Berlin Congress, 1890; Virchows Arch. f. path. Anat. **136**:1, 1894.

86. Metchnikoff: Virchows Arch. f. path. Anat. **107**:209, 1887.

transference through animals. Again, many rabbits are insusceptible to infection with virulent streptococci. And lastly, many laboratory workers insist on the fulfilment of Koch's postulates, in particular the reproduction in animals of the disease picture characteristic of the malady in human beings. Such reproduction is often impossible, since streptococci often show a directly opposite effect in the rabbit than the same strain originally produced in man. The immediate sequel to these irregularities was a discussion about the strict specificity of *Streptococcus erysipelatis,* repercussions of which are heard in most recent studies aiming to prove that *Streptococcus scarlatinae* and its toxic by-products are uniformly identical with *Streptococcus erysipelatis* and its toxic by-products.

Rosenbach,[87] in 1884, and Passet,[88] in 1885, were able to isolate streptococci from infections in wounds. They failed to differentiate between these organisms, called *Streptococcus pyogenes,* and the streptococci isolated from erysipelatous lesions. Morphologically, culturally and pathogenically all these various streptococci seemed identical.

Nicolaier and Guarnieri,[89] in 1886, isolated *Streptococcus septicus* from septicemia in human beings. Biondi [90] simultaneously described *Streptococcus septopyemicus* isolated in cases of septicemia in human beings. Flügge,[91] at this time, further confused the subject by naming a streptococcus also isolated from septicemia and septic wounds *Streptococcus pyogenes-malignus.*

Widal,[92] Verneuil and Clado,[93] and E. Fraenkel,[94] in 1889, Achalme,[47] in 1892, Petruschky,[95] in 1894, and Marmorek,[96] in 1902 firmly believed that streptococci isolated from erysipelas and puerperal fever were identical. These authors also believed that typical erysipelatous lesions could be produced in rabbits equally well with streptococci isolated from non-erysipelatous origins.

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87. Rosenbach: Mikroorganismen bei der Wundinfektionskrankheiten des Menschen, Wiesbaden, 1884, chapter XXII.

88. Passet: Fortschrift der Medicin, 1885, vol. 3.

89. Nicolaier and Guarnieri, in Flügge: Die Mikroorganismen, ed. 2, 1886, p. 154.

90. Biondi: Ztschr. f. Hyg. **2**:194 and 225, 1886; Riforma med., 1886, no. 3.

91. Flügge: Die Mikroorganismen, Leipzig, 1896, p. 106.

92. Widal: Etude sur l'infection puerperale, phlegmasia alba dolens et l'erysipele, Paris, 1889.

93. Verneuil and Clado: Compt. rend. Acad. d. sc. **108**:714, 1889.

94. Fraenkel: München. med. Wchnschr. **52**:548, 1868; Centralbl. f. Bacteriol. **6**:691, 1889; Virchows Arch. f. path. Anat., 1902, vol. 167.

95. Petruschky: Ztschr. f. Hyg. u. Infektionskrankh. **17**:59, 1894; **18**:413, 1894; **22**:485, 1896; **23**:142, 1896; Centralbl. f. Bakteriol **17**:560, 1895.

96. Marmorek: Compt. rend. Soc. de biol. **47**:123 and 230, 1895; ibid. **50**:1096, 1898; Ann. de l'inst. Pasteur **9**:593, 1895; ibid. **16**:169 and 172, 1902.

The specificity of *Streptococcus erysipelatis* was further challenged by Bonome,[97] Jordan,[98] Jochmann,[99] Reiche,[100] Schomerus,[101] Marbaix[102] and Petruschky[95] who described cases of erysipelas due to staphylococci. The confusion increased when Neufeld[103] and von Leube[104] observed that the pneumococcus could also be isolated from the erysipelatous lesion. These authors reported that they were successful in producing experimental erysipelas by the injection in animals of the pure culture of pneumococci.

Although during this time the relationship of *Streptococcus erysipelatis* was never seriously challenged, yet the belief grew rapidly among bacteriologists that all strains of streptococci isolated from septic conditions could be classified under the group name of *Streptococcus pyogenes*.

Bulloch,[105] in 1896, scouted the idea that different species of streptococci existed. This author advanced clinical and experimental evidence to show that the great variety of lesions produced by the type *Streptococcus pyogenes* could be explained to reside in four main factors influencing the various pathologic lesions, namely, (1) variability in virulence of the organism; (2) variation in the site and depth of the infection; (3) variation in resistance on the part of the body, and (4) the association of *Streptococcus pyogenes* with other microbes, pathogenic and nonpathogenic.

Out of this hopelessly confused polemic and inability to distinguish varieties of streptococci by their morphology and pathogenicity, new methods developed for the identification of these organisms by cultural characteristics and biochemical reactions. Schottmueller,[106] in 1903, classified streptococci on their morphology and the appearance of the cultures on human blood-agar plates. By these methods Schottmueller recognized two main groups, namely, *Streptococcus longus* or *hemolyticus*, the more virulent type which produced hemolysis on blood medium, and *Streptococcus mitior* or *viridans*, which included the less virulent strains and which produced green, nonhemolyzing colonies on blood medium.

97. Bonome: Centralbl. f. Bakteriol. **8**:172 and 703, 1890.

98. Jordan: Arch. f. klin. Chir. **42**:325, 1891; München. med. Wchnschr. **48**: 1371, 1901.

99. Jochmann: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **16**:76, 1906; Deutsche med. Wchnschr., 1909, p. 2103.

100. Reiche: Jahrb. d. Ham. Staatskrankenanst. **12**:289, 1907.

101. Schomerus: Jahrb. d. Ham. Staatskrankenanst. **12**:289, 1907.

102. Marbaix: Cellule **8**:1, 1892.

103. Neufeld: Ztschr. f. Hyg. u. Infektionskrankh. **36**:254, 1901.

104. Von Leube: Therapie d Gegenw. **7**:1, 1906; Sitzungsb. d. phys.-med. Gesellsch. zu Wurzb., 1906, p. 18.

105. Bulloch: Lancet **1**:982, 1896.

106. Schottmueller: München. med. Wchnschr. **1**:849, 894 and 909, 1903.

Smith and Brown,[107] in 1914, and Brown,[108] in 1919, invented another classification, naming *Streptococcus hemolyticus* "Beta" type, and *Streptococcus viridans* "Alpha" type.

Other authors suggested a large array of sugar fermentation reactions for the identification of types of streptococci. Notable contributions along these lines are the studies of Holman[109] and Andrewes and Horder.[110]

However, none of these new methods were found to serve as reliable criteria by which type specificities within the large group of *Streptococcus hemolyticus* could be detected. Most of the streptococci isolated from widely different pathogenic sources, such as erysipelas, scarlet fever angina, mastoiditis, sinusitus, septic sore throat, osteomyelitis and bronchopneumonia, and even from throat secretions of patients with diphtheria apparently corresponded to Brown's "Beta" type streptococcus or Holman's *Streptococcus pyogenes*.

The recent development of serologic methods so successfully employed for the demonstration of type specificities within the group of the typhoid-dysenteri-coli bacilli rapidly found their usefulness when applied to the large group of *Streptococcus hemolyticus*.

IMMUNOLOGIC PERIOD

OPSONIC INDEX

Many investigators have already demonstrated that serum from normal human beings does not possess streptococcidal powers. The disappearance of streptococci from the blood or tissues, therefore, could not be explained by the assumption that the serum loses something during the height of the disease, but regains this substance as convalescence sets in and at that time destroys the streptococci.

According to Metchnikoff,[86] Denys and Leclef,[111] Bordet,[112] Marchand[113] and others, this agent was believed to be found in the phagocytes. Following close on the discovery of this immunologic phenomenon, Wright and Douglas[114] observed that during acute attacks

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107. Smith and Brown: J. M. Research **31**:455, 1914-1915.

108. Brown: Monographs of the Rockefeller Institute for Medical Research, 1919, no. 9; J. Exper. Med. **31**:35, 1920.

109. Holman: J. Infect. Dis. **15**:209, 227 and 293, 1914; J. M. Research, **34**: 377, 1916. Holman, Avery, Kinsella and Brown: J. Lab. & Clin. Med. **3**:618, 1918.

110. Andrewes and Horder: Lancet **2**:708, 775, 780 and 852, 1906.

111. Denys and Leclef: Cellule **11**:177, 1895; Centralbl. f. Bakteriol. **24**:685, 1898.

112. Bordet: Annal. de l'inst. Pasteur **11**:177, 1897; Traite de l'immunite, Paris, 1920.

113. Marchand: Arch. de méd. expér. et d'anat. path. **10**:253, 1898.

114. Wright and Douglas: Proc. Roy. Soc. London **74**:147, 1905.

of furunculosis and sycosis, as well as other staphylococcic infections, the opsonins rapidly diminished in the patient's blood serum. By treating such persons with staphylococcic vaccine these authors were able to increase greatly the opsonic index and, in that manner, to reduce the period of hospitalization of persons afflicted with staphylococcic infections.

Shortly after the appearance of these studies, Ruediger,[115] in 1906, found that the fluid expressed from the bullae of patients with erysipelas did not contain streptococcidal powers. This author soon became aware that destruction of streptococci in defibrinated blood was brought about by the leukocytes present after these had been acted on by the opsonins contained in the patient's blood serum. Thus he observed that phagocytosis or destruction of streptococci could not take place with washed leukocytes. However, during the course of erysipelas, the opsonic index was increased and, with few exceptions, the streptococcidal power in the patient's serum was roughly proportional to the leukocytosis. This study had more than theoretical significance, in that it definitely indicated the practical application of this phenomenon in preventive measures and possible cures of streptococcic infections.

Similar results were obtained by Schorer,[116] in 1907, in a study of the opsonic index in thirty-six patients with erysipelas who were not treated, and thirty-seven patients with erysipelas who were treated, with one or more injections of a uniform mixture of killed streptococcic cultures obtained from four patients with erysipelas. In most of the untreated patients the opsonic index increased during the first three days of the disease, and the rise was then followed by a sudden fall. The injections of killed streptococci caused, on the whole, a rapid increase of the opsonic index. A relation between the elevation of the opsonic index and the improvement of the patients, however, was not observed. The apparent shortening of the duration of the disease in the vaccinated persons suggested that the artificial increase of the opsonins was of some value.

Simultaneously with this study, Tunnicliff[117] obtained the same results during the course of scarlet fever. In 1908, she applied the same study to the opsonic index during erysipelas, but left the question of the specific nature of her results undetermined. As late as in 1920, she renewed the study of the opsonic index in both scarlet fever and erysipelas. She concluded that the serum from an acute case of erysipelas was found to contain opsonins and agglutinins for the streptococci

115. Ruediger, G. F.: J. Infect. Dis. **3**:755, 1906; Further Studies on Streptococcus Infections, J. A. M. A. **46**:108 (Jan. 13) 1906.

116. Schorer: Am. J. M. Sc. **134**:728, 1907.

117. Tunnicliff, Ruth: J. Infect. Dis. **4**:304, 1907; ibid. **5**:268, 1908; Further Studies on the Specificity of the Streptococci, J. A. M. A. **75**:1339 (Nov. 13) 1920.

isolated from erysipelas, but not for hemolytic streptococci isolated from other sources, such as scarlet fever, otitis media, influenza and puerperal sepsis. The results of agglutinin-absorption tests confirmed her results with the opsonic index. These facts suggested to Tunnicliff that the hemolytic streptococci from erysipelas formed a distinct group of microorganisms, which completely removed the opsonins for these cocci, while absorption with scarlatinal strains did not have any such effect. At this time Tunnicliff asserted that the erysipelas streptococci belong to a distinct immunologic group, as determined by opsonification and agglutination. It is regrettable that the series of experiments which served as the basis for such an important assertion of strict specificity of *Streptococcus erysipelatis* was not larger.

As early as in 1910, Boughton,[118] by means of the opsonic index, had observed results in erysipelas which were similar to those described by Ruediger, Schorer and Tunnicliff, but this investigator did not come to definite conclusions about the specific nature of the immunologic reactions observed.

COMPLEMENT FIXATION

By further immunologic studies of strains of hemolytic streptococci isolated from erysipelas, it became increasingly evident that these organisms presented certain biologic characteristics which separated these strains from the large heterogeneous group of *Streptococcus hemolyticus* commonly associated with a great variety of pathogenic processes. The first attempt to classify erysipelas streptococci by means of the complement-fixation reaction was undertaken Livierati [119] in 1907. This investigator tested the serums obtained in eighteen cases of scarlet fever with the following antigens: streptococci isolated from scarlet fever and erysipelas, staphylococci, diplococci and the typhoid bacillus. He observed that all the scarlet fever serums gave positive fixation with the scarlet fever streptococcus antigens, and negative results with the other antigens.

Uffenheimer,[120] in 1909, repeated this work and confirmed the specific fixation reaction between scarlet fever serums and scarlet fever antigens. Incidentally, he also observed that the complement-fixation reaction was strongest on the tenth day of the disease.

Foix and Mallein,[121] in 1907, and more extensively in 1910, obtained similar results with scarlet fever serums and antigens. In a careful study of serums obtained from patients ill with erysipelas and puerperal sepsis, these authors observed that the two serums gave negative fixation reactions with scarlet fever antigens.

118. Boughton: Tr. Chicago Path. Soc. **8**:24, 1909; J. Infect. Dis. **7**:110, 1910.
119. Livierati: Centralbl. f. Bakteriol. **50**:422, 1909; Gazz. d. osp. **28**:835, 1907.
120. Uffenheimer: München. med. Wchnschr. **56**:2471, 1909.
121. Foix and Mallein: Presse méd. **15**:777, 1907; ibid. **18**:215, 1910.

Castex,[122] in 1909, employed serums obtained from patients with erysipelas, scarlet fever, abscesses, puerperal sepsis, pleurisy and arthritis, and he employed as antigens strains of streptococci isolated from patients with scarlet fever. This investigator obtained positive fixation reactions with every one of the serums except three scarlatinal serums. He concluded, therefore, that specific antibodies were not produced by any of these various streptococci.

Dopter and Sacquepee,[123] in 1914, corroborated the results obtained by Castex and concluded that strains from septicemia, erysipelas and scarlet fever all had a common fixation property. Schleissner,[124] in 1909, on the other hand, adhered to the specific complement-fixation reaction in scarlet fever serums with scarlet fever streptococcic antigens, while he found that *Streptococcus erysipelatis* antigens gave negative reactions with the scarlatinal serums.

Howell,[125] in 1918, reported an extensive study of the complement-fixation reaction in an attempt to classify sixty-five strains of streptococci isolated from cases of anterior poliomyelitis, erysipelas, scarlet fever, endocarditis and other definite disease entities. After an exhaustive study she concluded that only a slight correlation was to be found between the complement-fixation reactions and grouping based on the disease from which the organisms were isolated. Howell concluded that classification of streptococci on the basis of this test could not be justified. She made exception, however, in the more definite disease groups, such as anterior poliomyelitis, erysipelas and endocarditis, and stated that the complement-fixation reaction tended toward group specificity in these diseases.

Andersen,[126] in 1926, in a study of eighty-eight strains of hemolytic streptococci isolated from a variety of infections in human beings, sixty-one of which were from scarlet fever and five from erysipelas, abandoned the use of agglutination tests for their classification, mostly on account of technical difficulties. He finally adopted the complement-fixation reaction. He concluded from a large study that the scarlet fever streptococci formed a fairly specific group and that a serum prepared against *Streptococcus erysipelatis* was absorbed by nine heterogeneous streptococci, five of which were isolated from patients with erysipelas.

Although the complement-fixation reaction gives more promising results as to type specificities within the large group of *Streptococcus*

122. Castex: Presse méd. **17**:324, 1909,

123. Dopter and Sacquepee: Précis de Bacteriologie, Paris, Ballière & Sons, 1914.

124. Schleissner: Centralbl. f. Bakteriol. **44**:676, 1909; Wien. klin. Wchnschr. **22**:553, 1909.

125. Howell: J. Infect. Dis. **22**:230, 1918.

126. Andersen: Compt. rend. Soc. de biol. **95**:1690, 1926.

hemolyticus than do other methods of differentiation, however, further elaboration is indicated before this test can be relied on for the determination of such types of organisms as *Streptococcus scarlatinae* and *Streptococcus erysipelatis*.

PRECIPITIN

Numerous attempts have been made to classify erysipelas streptococci, as well as heterogeneous strains of streptococci, by means of precipitin reactions. Marmorek,[127] in 1898, is reported by Tchistowitch to have employed this test for the purpose of differentiation of streptococcic strains. Barnes,[128] in 1919, reported that he was able to obtain specific precipitin reactions with streptococci. Krumwiede and Valentine,[129] in 1921, scouted the specificity of precipitin reactions when applied to streptococci and stated that the results obtained by this method were identical with those obtained by the ordinary agglutination tests. Although there seemed to be some immunologic grouping of hemolytic streptococcic strains by means of complement fixation, opsonification, agglutination and absorption of agglutinins, Hitchcock,[130] in 1924, reported that the group of hemolytic streptococci is homogeneous when studied with the precipitin reaction.

Coleman and Wheeler,[131] in 1926, demonstrated that an extract prepared by heating the sediment of an eight day broth culture of *Streptococcus scarlatinae* (Dochez) gave a positive precipitin reaction with the homologous immune rabbit serums employed in the agglutination tests. Precipitinogens prepared by the same method from four streptococcic strains, one of which was a strong toxin producer, gave strongly positive reactions with these serums.

Rosenow,[132] in 1926, reported specific precipitin reactions in the diagnosis of scarlet fever, erysipelas, poliomyelitis and other conditions due to streptococcic infections.

AGGLUTINATION AND AGGLUTININ ABSORPTION

The importance of the problem of unity or multiplicity within the large group of hemolytic streptococci is readily understood by the increasing array of new methods developed for the detection of specific types of streptococci. Besides the purely scientific motive behind the studies, much of the work has been largely prompted by a desire on the part of

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127. Marmorek, reported by Tchistowitch: Ann. de l'inst. Pasteur **13**:406, 1899.

128. Barnes: J. Infect. Dis. **25**:47, 1919.

129. Krumwiede and Valentine: J. Immunol. **6**:343, 1921.

130. Hitchcock: J. Exper. Med. **40**:445, 1924.

131. Coleman and Wheeler: J. Lab. & Clin. Med. **11**:1181, 1926.

132. Rosenow, E. C.: Precipitin Reaction in Diagnosis of Scarlet Fever and Allied Hemolytic Streptococcus Infections, J. A. M. A. **86**:9 (Jan. 2) 1926.

the physician to discover effective measures of specific treatment and control of many perplexing infectious diseases.

In reviewing the immense work accumulated on classifications of the hemolytic streptococci, one is struck by the fact that existing specificities of streptococci associated with scarlet fever, erysipelas, puerperal sepsis and other streptococcic infections, have not been convincingly established by the methods of morphologic study, sugar fermentations, hemolysis of blood cells, opsonification, complement-fixation or precipitin reactions.

When one reviews the methods of agglutination and animal protection tests, one immediately enters on a series of studies exceedingly fruitful in the grouping of streptococci.

According to von Lingelsheim,[133] the first agglutination test performed with streptococci placed against antistreptococcic serum is credited to Van de Velde [134] in 1898. Almost coincidentally, Kraus and Loew [135] discovered that the serum of patients vaccinated with dead streptococcic cultures agglutinated these organisms in vitro.

Salge and Hosenknopf,[136] in 1902, immunized animals with scarlet fever streptococci and found that the immune serum agglutinated these organisms in a titer of 1 to 500 dilution. The low titer is no doubt due to a brief course of active immunization of the animals. This work was repeated at once by Moser and Pirquet,[137] who reported that their scarlet fever antistreptococcic serum prepared in horses agglutinated scarlet fever streptococci in dilutions of 1 to 50,000.

Neufeld,[138] in 1903, repeated this work, and employed highly agglutinating serums that were also prepared in horses immunized with injections of streptococci which had not been subcultured on artificial mediums. Aronson,[139] in the same year, corroborated these observations, and was also able to cross-agglutinate streptococcic strains from various sources. By this method he detected that scarlet fever streptococci formed a specific homogeneous group of organisms.

The most extensive study of agglutination of *Streptococcus hemolyticus* was undertaken by Dochez, Avery and Lancefield [140] in 1919. These authors made an exhaustive biologic study of 125 strains of hemolytic

133. Von Lingelsheim: Beitr. z. Exper. Therap. **1**:1, 1899; Kolle and Wassermann's Handbuch der pathogenen Mikroorganismen, ed. 1, Jena, 1903, vol. 3, p. 303.

134. Van de Velde: Monatschr. f. prakt. Tierh. **2**:97, 1897; Arch. de méd. expér. et d'anat. path., referred to in Hyg. Rundschau, 1898, p. 1188.

135. Kraus and Loew: IX Internat. Kong. f. Hyg., Madrid, 1898.

136. Salge and Hosenknopf: München. med. Wchnschr. **49**:1729, 1902.

137. Moser and Pirquet: Centralbl. f. Bakteriol. **34**:560 and 714, 1903.

138. Neufeld: Ztschr. f. Hyg. **44**:161, 1903.

139. Aronson: Berl. med. Wchnschr. **39**:369, 979 and 1006, 1902; Centralbl. f. Bakteriol. **34**:444, 1903.

140. Dochez, Avery and Lancefield: J. Exper. Med. **30**:179, 1919.

streptococci collected in a limited community during the course of what appeared to be an epidemic of bronchopneumonia secondary to measles. All the strains were studied as to their cultural characteristics, bile solubility, capacity to hemolyze blood cells, carbohydrate fermentation reactions and, finally, antigenic differences existing between strains of *Streptococcus hemolyticus*. These authors concluded that immunologic differences exist between strains of hemolytic streptococci of the human type, and that four biologic types can be identified by means of reactions of agglutination, agglutinin absorption and protection. Further study revealed that at least two other types were encountered, and indications were elicited that more types existed.

Havens,[141] in 1919, employed the agglutination test in a study of 292 strains of hemolytic streptococci obtained from a great variety of pathologic conditions in human beings. Following a series of experiments with active immunization in rabbits, this author concluded that 93 per cent of the strains studied fell into three fairly definite groups which could readily be differentiated serologically, as well as by mice protection tests.

In rapid succession there appeared a series of most revolutionizing studies bearing on the apparent strict specificity of the scarlet fever streptococcus. Notable work on this discovery was contributed by Bliss,[142] Tunnicliff,[143] Dochez and Bliss,[144] Gordon,[145] the Dicks [146] and Eagles.[147] The combined efforts of these investigators proved beyond any reasonable doubt that *Streptococcus scarlatinae* constitutes a definitely specific and antigenically compact group of organisms, differentiable by agglutination, agglutinin absorption and protection tests, from other strains of hemolytic streptococci, isolated from patients with erysipelas, septicemia and puerperal fever.

Dick and Dick, in 1924, further observed that *Streptococcus scarlatinae* produced a demonstrable soluble toxin, which, when injected into animals and man, stimulated the production of a specific antitoxin.

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141. Havens: J. Infect. Dis. **25**:315, 1919.

142. Bliss: Bull. Johns Hopkins Hosp. **31**:173, 1920; J. Exper. Med. **36**:575, 1922.

143. Tunnicliff, Ruth: Specific Nature of Hemolytic Streptococcus of Scarlet Fever, J. A. M. A. **74**:1386 (May 15) 1920; Further Studies on Specificity of Streptococci, ibid. **75**:1339 (Nov. 13) 1920.

144. Dochez, A. R., and Bliss, W. P.: Biologic Study of Hemolytic Streptococci from Throats of Patients Suffering from Scarlet Fever, J. A. M. A. **74**: 1600 (June 5) 1920.

145. Gordon: Brit. M. J. **1**:632, 1921.

146. Dick, G. F., and Dick, G. H.: Experimental Inoculations in Scarlet Fever, J. A. M. A. **77**:782 (Sept. 3) 1921; Experimental Scarlet Fever, ibid. **81**: 1166 (Oct. 6) 1923; Etiology of Scarlet Fever, ibid. **82**:301 (Jan. 26) 1924.

147. Eagles: Brit. J. Exper. Path. **5**:199, 1924.

Dochez,[148] in 1924, employed both the toxic principle and the living culture of the scarlet fever streptococci in the production of a therapeutic scarlet fever antitoxin. For this reason, Dochez' antiserum proved more potent in the treatment of scarlet fever than that produced by the Dicks with the toxin alone.

The tremendous interest displayed everywhere in the study of scarlet fever was soon the means of making antitoxin treatment in scarlet fever popular. The medical world hails the beneficient therapeutic results obtained with the scarlet fever antitoxin. This achievement in American medicine was largely accomplished by the indications of type specificity of scarlet fever streptococci, as demonstrated by the agglutination and agglutinin absorption tests.

In a study of the hemolytic group of streptococci associated with erysipelas, the only indication of type specificity by means of agglutination and agglutinin absorption was that advanced by Tunnicliff[117] in 1920. Birkhaug,[149] in 1924, subjected the erysipelas streptococcic group to an extensive study by means of morphologic, cultural and biologic methods. Thirty-four strains of hemolytic streptococci were isolated from typical erysipelatous lesions. Nine of these strains were obtained from the serous fluid aspirated from the cutaneous and subcutaneous tissues within the erysipelatous lesion. Seventeen strains were obtained by the following technic: 0.5 to 1 cc. of physiologic sodium chloride solution was injected intradermally and subdermally along the margin of the erysipelatous lesion. This produced a small bleb from which fluid was immediately aspirated without a withdrawal of the needle. The fluid withdrawn was at once mixed with melted blood-agar and poured into Petri dishes, according to the method suggested by Brown.

Pure cultures of *Streptococcus hemolyticus* were present in 91 per cent of the plates poured with the fluid aspirated from the margin of the erysipelatous lesion. Similar cultures were made from the fluid withdrawn from the less inflamed, central portion of the erysipelatous lesion. These cultures yielded streptococci in only 46 per cent of the poured blood-agar plates.

The streptococci isolated from patients with erysipelas did not differ morphologically or culturally from the strains isolated from heterogeneous sources. Agglutination reactions were then resorted to for the determination of possible immunologic groupings of the erysipelas strains.

Before an attempt was made to produce agglutinins in rabbits with the erysipelas streptococci, every animal employed was tested carefully for the presence of natural agglutinins against a series of strains to be used in the active immunization of these animals. Among the stock

148. Dochez: Proc. Soc. Exper. Biol. & Med. **21**:184, 1924.

149. Birkhaug: Proc. Soc. Exper. Biol. & Med. **22**:292, 1925; Bull. Johns Hopkins Hosp. **36**:248, 1925.

rabbits, 23 per cent were found to possess natural agglutinins for the erysipelas streptococci. These animals were consequently discarded.

Three methods of inoculation were employed for the production of immune serum: (1) intravenous; (2) intracutaneous, and (3) intracutaneous in previously injected agar (Dochez' method). The last mentioned method yielded a titer of 1 to 5,120 after from ten to twelve weeks' immunization. Seven serums were prepared in this manner with seven strains of hemolytic streptococci isolated from seven different patients with severe erysipelas. The employment of seven individual serums was decided on in order to detect groupings within a possible type of erysipelas streptococci.

Altogether, thirty-four strains of erysipelas streptococci were employed in the tests of agglutination and agglutinin absorption. Some of these strains were isolated in New York, Boston, Washington, D. C., and Baltimore. By these tests it was demonstrated that of the thirty-four erysipelas strains, thirty-one, or 91.2 per cent, were agglutinated and cross-absorbed with each of the seven immune erysipelas serums, indicating strongly that the erysipelas streptococcus constitutes a compact specific group of micro-organisms.

An attempt was made at that time to ascertain whether a possible serologic relationship existed between the hemolytic streptococci isolated from patients with erysipelas and hemolytic streptococci isolated from patients with scarlet fever angina. Twenty-three scarlatinal strains were studied and no apparent group relationship was found to exist between these two large groups of hemolytic streptococci.

Forty-five strains of miscellaneous hemolytic streptococci were isolated from pyogenic infections other than erysipelas. These strains were employed in cross-agglutination tests against seven immune erysipelas serums. The conditions from which these streptococci were isolated included cellulatis, dermatitis, empyema, mastoiditis, meningitis, nasal sinusitis, peritonitis, puerperal sepsis, tonsillitis and surgical wounds. Nine strains, or 20 per cent, were agglutinated with the erysipelas serums. The majority of miscellaneous agglutinable strains were isolated from patients with nasal streptococcic infections.

These studies indicated that it was possible, by immunologic methods, to differentiate a group of hemolytic streptococci causing erysipelas lesions from hemolytic streptococci causing scarlet fever and other streptococcic infections.

Eagles,[147] in 1924 and 1926,[150] demonstrated that hemolytic streptococcic strains from patients with scarlet fever and erysipelas formed distinct immunologic groups, and that puerperal hemolytic streptococci also formed a separate group of organisms by agglutination methods.

150. Eagles: Brit. J. Exper. Path. **7**:286, 1926.

This investigator detected a slight antigenic relationship between these three groups of hemolytic streptococci, in that some of these strains overlapped by agglutination with strains of the other groups.

Stevens and Dochez,[151] in 1926, corroborated the agglutination results of Tunnicliff, Eagles and Birkhaug, and reported that erysipelas strains formed a closely related group of hemolytic streptococci, equally as compact as the scarlatinal group, although the two groups were related antigenically, but less closely related than the strains within the groups.

LOCAL PASSIVE IMMUNITY

Birkhaug,[152] in 1925, extended the study of the biology of *Streptococcus erysipelatis* to a demonstration of antigenic relationships in this group by a series of studies of local passive immunity in the rabbit. These studies were undertaken because of much debate concerning the reliability of such immune reactions as agglutination and agglutinin absorption for the purpose of determining type specificities among strains of hemolytic streptococci. The method resorted to in these protection tests was that suggested by Rivers [153] and Rivers and Tillett,[154] in 1925, for demonstration of antigenic relationships of bacteria in vivo.

That the skin possesses a special biologic function not shared by other tissues in the body was suggested by Besredka,[155] Gay,[156] Mironesco [157] and others. Rivers and Tillett, in 1925, demonstrated that small areas of skin infiltrated with an immune monovalent streptococcic serum produced local protection against the culture of hemolytic streptococcus employed for the production of the serum.

In the study of the phenomenon of local passive immunity, Birkhaug employed twenty-five normal rabbits susceptible to intradermal infection with hemolytic streptococci. The blood serum of these animals was first tested for the presence of natural agglutinins for the cultures of streptococci employed in these experiments. The depilated skin on each animal was then divided into seven squares of about 3 to 4 sq. cm. Into the center of each area 0.1 cc. of one of the seven immune erysipelas serums was infiltrated intradermally. Twenty-four hours later, 0.1 cc. of a twenty-four hour broth culture of one of the erysipelas streptococci was injected intradermally into the center of each of the seven immunized areas on either side of the body.

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151. Stevens and Dochez: J. Exper. Med. **44**:439, 1926.
152. Birkhaug: Bull. Johns Hopkins Hosp. **37**:85, 1925.
153. Rivers: J. Exper. Med. **41**:179, 1925.
154. Rivers and Tillett: J. Exper. Med. **41**:185, 1925.
155. Besredka: Tr. Roy. Soc. Trop. Med. & Hyg. **17**:346, 1923-1924; Presse méd. **32**:585, 1924.
156. Gay: Physiol. Rev. **4**:191, 1924.
157. Mironesco: Compt. rend. Soc. de biol. **92**:293, 1925.

When all the seven immune erysipelas serums were used individually, it was observed by means of the phenomenon of local passive immunity produced in the skin of rabbits that thirteen of fourteen cultures of *Streptococcus erysipelatis,* or 93 per cent, did not produce visible lesions. This observation was in accord with the results obtained with the agglutination and agglutinin absorption tests. The immune erysipelas serums offered little or no local protection against the injurious action of virulent cultures of nonerysipelatous hemolytic streptococci. Birkhaug concluded that by this method it is possible to differentiate a group of hemolytic streptococci causing erysipelas from other groups of streptococci responsible for scarlet fever and pyogenic lesions in general.

GENERAL PASSIVE IMMUNITY

Extending the studies on local passive immunity to include general passive immunity, Birkhaug,[158] in 1925, injected large amounts of immune erysipelas serum from rabbits, intravenously or subcutaneously, in suspectible rabbits; twenty-four hours later the animals were injected with lethal doses of *Streptococcus erysipelatis* either intravenously or subcutaneously. Complete protection was obtained in most instances when the proper dosage of immune serum was placed against graduated doses of the virulent erysipelas streptococci. Normal rabbit serum or the erysipelas immune serum heated for one hour at 60 C. failed to offer similar protection against the fatal effects of the erysipelas streptococci. These studies indicated a definite promise for the specific treatment of erysipelas in human beings.

EXPERIMENTAL ERYSIPELAS

The early studies on experimental erysipelas in rabbits by Orth,[57] Pitoy,[58] Fehleisen [69] and numerous other investigators were adequately corroborated by Gay and Rhodes,[159] in 1922, and by Rivers and Tillett,[160] in 1925. None of the previously mentioned experimenters, however, had employed strains of *Streptococcus erysipelatis* which had been classified biologically by means of agglutination, and agglutinin-absorption tests, although it is reasonable to suppose that these investigators were dealing with typical erysipelatous streptococci.

In a long series of experiments, Birkhaug,[158] in 1925, was able to reproduce typical erysipelas-like lesions in normal and susceptible rabbits by inoculating these animals intradermally with agglutinable strains of *Streptococcus erysipelatis.* Three types of lesions were observed—erythematous, diffuse and phlegmonous erysipelas. The pathologic pic-

158. Birkhaug: Bull. Johns Hopkins Hosp. **37**:307, 1925.

159. Gay and Rhodes: J. Infect. Dis. **31**:101, 1922.

160. Rivers and Tillett (footnotes 153 and 154).

ture of the erythematous and diffuse lesions was similar to that seen in cases of erysipelas in human beings. Amoss and Bliss,[161] in 1927, repeated these studies.

BLANCHING

Birkhaug,[158] in 1925, was able to demonstrate the Schultz-Charlton blanching phenomenon in the erysipelatous lesions by the intradermal injection of 0.5 cc., and the subcutaneous injection of 1 cc., of immune erysipelas serum. The blanching usually occurred in the course of twenty-four hours following the injection, and persisted for about fifteen hours. Dochez' antiscarlatinal serum injected in a similar manner on the other side of the erysipelas lesion failed to produce any blanching.

This observation was confirmed by Singer and Kaplan,[162] in 1926, who reported that they were able to obtain 50 per cent of blanching phenomena of erysipelas lesions by the use of serums obtained from human beings actively immunized with the toxin produced by *Streptococcus erysipelatis*. Erysipelas serum from convalescent patients failed to produce this phenomenon, because of its low antitoxin concentration.

SOLUBLE TOXIN

As early as in 1888, Manfredi and Traversa [163] studied the action of toxic products in the filtrate of erysipelas streptococcic cultures. These investigators inoculated peptonized bouillon with pure cultures of the erysipelas streptococci and incubated the broth at temperatures varying between 27 and 30 C., under aerobic as well as anaerobic conditions. After eight days' incubation, the cultures were passed through a Ton filter. Their report did not state whether or not the filtrate was completely freed from bacterial cells. The filtrate was injected into guinea-pigs, rabbits and frogs. These animals showed typical symptoms and signs of bulbar paralysis, with delirium and convulsions before death, which usually occurred on the second day after inoculation. The filtrate obtained from the cultures grown under anaerobic conditions proved much more toxic to these animals than that produced under aerobic conditions.

Achalme,[47] in 1892, repeated this work and, on the whole, found the same nervous symptoms produced by the toxic filtrate in guinea-pigs, rabbits and frogs. The frog, in particular, reacted more violently to the toxin than the other animals.

Simultaneously with this work, Roger [164] was able to demonstrate that the filtrate of erysipelas streptococcic anaerobic cultures, grown for

161. Amoss and Bliss: J. Exper. Med. **45**:411, 1927.

162. Singer, H. A., and Kaplan, B.: Streptococcus Erysipelatis Toxin and Antitoxin, J. A. M. A. **87**:2141 (Dec. 25) 1926.

163. Manfredi and Traversa: Gior. internaz. d. sc. med. **10**:456, 1888.

164. Roger: Compt. rend. Soc. de biol. **1**:671, 1889; Rev. de méd., 1895; **15**:500, 1895; ibid. **16**:192, 1896.

five days at 30 C. was lethal for rabbits, from 15 to 20 cc. per kilogram of weight killing the animals in the course of two days. Although many workers have since been able to demonstrate the production of soluble streptococcic exotoxins, these toxic filtrates have constantly failed to kill laboratory animals, even in doses excessive of 20 cc. per kilogram of weight. Roger, however, made the valuable observation that when the soluble toxic filtrate of *Streptococcus erysipelatis* was heated at 104 C. and subsequently injected intravenously in rabbits, the animals survived. He further observed that by the injections of doses varying from 5 to 30 cc., active immunity could be established against lethal doses of the unheated toxic filtrate. Roger allowed another lot of toxin to be precipitated with alcohol, and the residue, when injected into rabbits, proved rapidly to be lethal for the animals. Roger concluded from these studies that the filtrates of *Streptococcus erysipelatis* cultures contained two substances, one thermolabile at 104 C., precipitable with alcohol and toxic for animals, and the other thermostable at 104 C., and antigenic in nature in that it stimulated the production of active immunity against subsequent infection. The latter observation was the first demonstration of the antigenic nature of the soluble exotoxic principle produced by *Streptococcus erysipelatis*, a fact completely forgotten until it was rediscovered by Dick and Dick in 1923, in relation to the ability of the hemolytic streptococci isolated from scarlet fever angina to produce this same toxic and antitoxic principle. Unfortunately, this important discovery was completely overlooked by Roger himself, when in 1895, in association with Charrin,[165] he prepared antistreptococcic serum, not with the toxic principle, but with the whole streptococcic culture.

Toxic filtrates were also described by Marmier [166] in 1895, Baginsky and Sommerfeld [167] in 1900 and Mamorek [168] in 1902. These filtrates, when injected into guinea-pigs, were reported to produce rapid death. Aronson, in 1902, was able only occasionally to produce hemolytic streptococcic toxic filtrates lethal for laboratory animals. Simon,[169] in 1904, failed to confirm the results of earlier workers with the toxic filtrates. Braun,[170] in 1912, obtained only slightly toxic filtrates of hemolytic streptococcic cultures.

Savchencko,[171] in 1905, was the first investigator to scout the notion that streptococcic filtrates were atoxic because of their failure to produce pathogenic lesions in animals. The truth of this contention was at once

165. Charrin and Roger: Compt. rend. Soc. de biol. **2**:124 and 224, 1895.
166. Marmier: Ann. de l'inst. Pasteur **9**:568, 1895.
167. Baginsky and Sommerfeld: Berl. klin. Wchnschr. **37**:588, 1900.
168. Mamorek: Ann. de l'inst. Pasteur **16**:169, 1902.
169. Simon: Centralbl. f. Bakteriol. **35**:308 and 440, 1903-1904.
170. Braun: Centralbl. f. Bakteriol. **62**:383, 1919.
171. Savchencko: Russk. Vrach. **25**:797, 1905.

evident in 1924 when these toxic filtrates were injected intradermally in susceptible persons in connection with the work of Dick and Dick on scarlet fever.

Continuing his experimental studies in erysipelas, Birkhaug,[172] in 1925, demonstrated the production of a soluble exotoxin by *Streptococcus erysipelatis*. A careful study of thirty-four strains of agglutinable erysipelas streptococci revealed the fact that toxin production in tryptic medium digest was constant with all these strains. He found that after incubation at 37 C., for from five to six days, under aerobic conditions, most of the bacteria-free culture filtrates contained from 30,000 to 50,000 skin test doses per cubic centimeter. Birkhaug demonstrated the toxicity of streptococcic culture filtrates by injecting 0.1 cc. of a 1 to 1,000 dilution of the toxic filtrate, intradermally, in susceptible persons. In the course of twenty-four hours the diluted filtrates produced positive skin lesions similar to those obtained in the Schick and Dick tests.

The question arose immediately concerning the relationship of the toxic principles produced by *Streptococcus erysipelatis* and *Streptococcus scarlatinae*. This query was partly answered by Birkhaug when in 1926 he tested a group of children and adults simultaneously with the Dick toxin and the erysipelas toxin. Among a group of 407 persons tested, 52 per cent gave positive reactions to the Dick test, and 24 per cent gave positive reactions with the erysipelas toxin. Only 10 per cent of these persons gave simultaneously positive reactions to the Dick test and to erysipelas toxin. This definitely indicated that a difference existed between the erysipelas and scarlet fever toxin comparable with the serologic differences observed between the two groups of hemolytic streptococci.

During these studies, Birkhaug also noted that a toxic principle, identical with the toxin produced in vitro by *Streptococcus erysipelatis*, was circulating in the blood serum of the patient with erysipelas and was also detected in his urine during the acute stage of the disease, disappearing during convalescence. Shortly after the disappearance of the toxic principle from the patient's blood serum and urine, an antitoxic principle was demonstrable, which, when mixed with the erysipelas toxin, completely neutralized the toxic effects of the culture filtrate of *Streptococcus erysipelatis*. This interesting observation suggested an almost indisputable immunologic relationship between the disease itself and the toxin produced outside the human organism by *Streptococcus erysipelatis*. The next step pointed the way for the production of erysipelas antitoxin in higher animals which, it was hoped, possibly might accomplish curative results when employed in patients with erysipelas.

Eagles [150] and Andrewes,[173] in 1926, confirmed the ability of *Streptococcus erysipelatis* to form soluble toxic filtrates and to give positive

172. Birkhaug: Proc. Soc. Exper. Biol. & Med. **23**:201, 1925.

173. Andrewes: St. Barth. Hosp. J. **33**:181, 1926.

reactions in susceptible persons when injected intradermally. By testing the toxins produced by *Streptococcus scarlatinae* and *Streptococcus erysipelatis,* Andrewes concluded that the results definitely suggested, even if they did not finally prove, that different races of hemolytic streptococci, differing serologically, formed also different toxins.

Dochez and Stevens,[174] in 1927, also confirmed Birkhaug's claim of toxin production by *Streptococcus erysipelatis.* These authors concluded that cutaneous reactions may be obtained in man with filtrates of the hemolytic streptococcic strains from erysipelas. The reactions obtained with the majority of filtrates from these strains were not neutralized by scarlatinal serums, but were completely neutralized by serums prepared with erysipelas strains.

Dochez and Stevens extended these studies to include cutaneous reactions in rabbits during immunization with filtrates of strains from erysipelas. In addition, these investigators demonstrated that rabbits immunized with these filtrates were made cutaneously allergic, and that two periods of allergy were observed, an early and a late phase. The earliest reactions occurring in the first period of allergy could be neutralized by erysipelas immune serums.

On the whole, these studies corroborated Birkhaug's thesis of an apparent specific toxin produced by *Streptococcus erysipelatis.*

ERYSIPELAS ANTITOXIN

The first curative antistreptococcic serum against erysipelas was prepared by Charrin and Roger [165] in 1895; it has already been referred to. In rapid succession followed the production of a variety of polyvalent antistreptococcic serums, particularly for use in scarlet fever and puerperal sepsis. The most outstanding attempts in this direction were those of Marmorek [168] in 1895, Aronson [144] in 1896, Moser and Pirquet [137] in 1903, Savchencko [171] in 1905 and Dochez [148] and Dick and Dick [146] in 1924. In deference to the antitoxins prepared by Dochez and the Dicks, it should be stated that these scarlet fever antitoxins were prepared either from scarlatinal strains of hemolytic streptococci and their toxic by-products (Dochez) or from the toxic filtrate alone (Dick and Dick), on the almost universally accepted assumption that scarlet fever is produced by the toxin of *Streptococcus scarlatinae.*

Having confirmed the work of other investigators, and having demonstrated more extensively the existence of a specific type of hemolytic streptococcus as the etiologic agent in erysipelas, Birkhaug proceeded to immunize laboratory animals, a donkey and, later, a horse, against living cultures and toxic filtrates of *Streptococcus erysipelatis.* After a consistent regimen of active immunization of these animals for almost one

174. Dochez and Stevens: J. Exper. Med. **46**:487, 1927.

year, the serum pooled from the immunized animals was found to possess a high concentration of antitoxic and antibacterial substances, which, after careful animal experimentation, warranted its employment in cases of erysipelas.

In 1926, Birkhaug [175] reported the therapeutic records of sixty patients with erysipelas who, up to that time, had been treated specifically with *Streptococcus erysipelatis* antitoxin. The majority of the patients were moderately ill when first seen, while at least twenty were severely ill at the time of the specific therapy. The average of the unconcentrated antitoxin was 100 cc., and of the concentrated globulin fraction 15 cc. In only eight cases was more than one dose administered.

The dominant clinical effects of the specific serum therapy in erysipelas was the prompt improvement of the toxic depression of the patient. This was followed shortly by a rapid and almost dramatic drop in the temperature, pulse rate and respiration. The critical drop of temperature and pulse rate took place at from twelve to eighteen hours following the intramuscular injection of the antitoxin. The most striking clinical effect noted in the patients treated early in the disease, preferably before the third day, was a rapid disappearance and fading of the erysipelatous lesion and the absorption of the blebs and the pitting edema in the previously affected parts of the body. Although it was observed in the late stages of the disease that the temperature and pulse rate yielded by lysis to the antitoxic therapy, yet the amelioration of toxic depression was quite distinct within from twelve to eighteen hours after the injection of the antitoxin.

Musser,[176] in 1927, reported on the value of the erysipelas antitoxic treatment in eleven cases. There was a prompt amelioration of the toxic symptoms, a sharp drop in temperature and a rapid disappearance of the erysipelatous lesion. Musser concluded from this small series of cases that the erysipelas antitoxin offers a distinct method in the control of this disease.

In September, 1927, Symmers and Lewis [177] made an extensive study of the antitoxin treatment in erysipelas. In reviewing the 15,277 cases of erysipelas seen in Bellevue Hospital during the past twenty-three years, these authors stated that almost every conceivable form of treatment had been practiced, most treatments being based on the application of local remedies. None of the methods appeared appreciably to shorten

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175. Birkhaug, K. E.: Erysipelas, J. A. M. A. **86**:1411 (May 8) 1926; J. Infect. Dis. **42**:35, 1928.

176. Musser, J. H.: Treatment of Acute Infectious and Contagious Diseases with Especial Reference to Scarlet Fever, Erysipelas, Measles and Meningitis, J. A. M. A. **88**:1125 (April 9) 1927.

177. Symmers, D., and Lewis, K. M.: Antitoxin Treatment of Erysipelas, J. A. M. A. **89**:880 (Sept. 10) 1927.

the course of the disease. Within the year previous to that in which the report was made, 131 patients with erysipelas had been treated by the antitoxin method, while every alternate patient was treated by old methods. After a period of critical observation, Dr. Lusk, whose experience in the treatment of erysipelas, according to Symmers and Lewis, is larger than that of any other physician on the American continent, requested that all patients be treated by the antitoxin method. As a result of the antitoxin treatment, the mortality in erysipelas was reduced from 10.1 per cent to 5.3 per cent, and the patient's period of disability was reduced by slightly more than 50 per cent. This therapeutic benefit permitted a reduction in the nursing staff to the extent of about 60 per cent and effected a notable saving of bed linen and sleeping garments by doing away with the destructive effects of ointments and similar local applications. Symmers and Lewis concluded that "the antitoxin treatment of erysipelas marks an advance, the results of which are commensurate with those obtained in the treatment of diphtheria. As far as the immediate attack is concerned, erysipelas is now a vanquished disease."

Platou, Schultz and Collins,[178] in December, 1927, reported observations based on 155 patients with erysipelas, of whom thirty-five were treated with local applications, eighty with roentgen-ray irradiation, thirty with erysipelas antitoxin and ten with the roentgen rays and antitoxin combined. The erysipelas antitoxin reflected its value by the return to normal temperature and subsidence of symptoms in 2.2 to 3.8 days, respectively, as compared with 3.4 and 8 days, respectively, required in the control group. These authors also noted that there was less tendency of the disease to spread in patients treated by the antitoxin method than in those treated by local applications. They also observed that the mortality among the patients receiving erysipelas antitoxin was one fourth that recorded for the subjects in the control series.

Allan,[179] in 1928, reported from the Mayo Clinic 209 cases of erysipelas, in forty-three of which antitoxin therapy was used. His conclusions are essentially confirmatory of those mentioned previously, the mortality being reduced from 13.5 per cent in the control series to 2.3 per cent in the series treated with antitoxin.

Blackfan,[180] in a personal communication, in 1928, reported the results obtained with antitoxin among infants with erysipelas and concluded "that the streptococcus erysipelas antitoxin acts specifically in the treatment of young infants with erysipelas and is comparable to the use of antitoxin in scarlet fever, but if delayed until complications have developed, it is apparently ineffective."

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178. Platou, E. S.; Schlutz, F. W., and Collins, L.: Erysipelas, Am. J. Dis. Child. **34**:1030 (Dec.) 1927.

179. Allan: Proc. Staff Meetings Mayo Clinic **3**:23, 1928.

180. Blackfan: Personal communication to the author.

During the past two years, Birkhaug [181] has observed thirty-six infants with erysipelas, ranging in age from 2 weeks to 24 months, who were treated with the erysipelas antitoxin. When the antitoxin was administered during the first three days of the disease, recovery was prompt if adequate doses of the antitoxin were administered. Repeated injections of 5,000 units of antitoxin every twelve hours is advisable until there is a critical drop in temperature and pulse rate. Of the thirty-six treated infants, five died from complications. When one bears in mind the extremely high mortality among infants under 2 years of age, with erysipelas, one can safely say that the erysipelas antitoxin treatment has somewhat changed the grave prognosis of the disease.

ACTIVE IMMUNIZATION WITH SOLUBLE ERYSIPELAS TOXIN AGAINST RECURRENT ATTACKS OF ERYSIPELAS

The weightiest immunologic argument against the suggestion offered by a group of modern investigators that erysipelas and scarlet fever are both caused by antigenically related hemolytic streptococci, is that scarlet fever confers a permanent qualitative immunity on the persons attacked by that disease, whereas erysipelas has been known from antiquity to predispose the subject to recurrent attacks of the disease. That the incidence of recurrence in erysipelas is brought about because of the mildness of the initial attack is precluded, since most of the patients in whom the disease is habitual give histories of moderately severe attacks of extensive erysipelas, running an average course of from eight to fifteen days. Another pertinent argument against the unity of the scarlet fever and erysipelas streptococci is that among the almost numberless and diverse complications of scarlet fever, it is extremely rare, even in the severest form of angina, for erysipelas to develop. Schottmueller,[182] in criticizing adherents of the theory of streptococcic unity in the two diseases, finally emphasized the comparatively high and specific infectiousness of scarlet fever in contradistinguishing this disease entity from erysipelas and other streptococcic infections.

Mention has already been made of Roger's [164] observation, in 1892, that rabbits injected with small doses of heated toxic filtrates became resistant to subsequent infection with massive doses of the unheated toxin. In the course of a large series of immunologic studies on the etiology of erysipelas, Birkhaug [183] attempted to unravel the causation of recurrent attacks of the disease in patients with habitual erysipelas. He observed that during the acute stages of erysipelas the patient's skin

181. Birkhaug, K. E.: Antitoxin Treatment of Erysipelas in Infants, Am. J. Dis. Child. **35**:540 (March) 1928.

182. Schottmueller: Klin. Wchnschr. **6**:1692, 1927.

183. Birkhaug, K. E.: Erysipelas, J. A. M. A. **88**:885 (March 19) 1927.

reacted positively with ten skin test doses of *Streptococcus erysipelatis* toxin until about the tenth day of the disease, when the patient's skin reaction became negative to multiple skin test doses of toxin. He further noticed that simultaneously with the advent of skin immunity to the erysipelas toxin, the toxin that previously was isolated from the patient's blood serum and urine had completely disappeared and that a gradually increasing amount of antitoxin appeared in the patient's blood serum, which in proper mixtures completely neutralized the toxin produced by *Streptococcus erysipelatis.*

In following up the patients after their discharge from the hospital, Birkhaug observed that the active immunity conferred by the attack of erysipelas disappeared in some patients as soon as six weeks after the onset of the disease. This loss of antitoxic immunity was determined in these persons by repeated intradermal injections of ten skin test doses of the erysipelas toxin. Simultaneously with the advent of positive response with the ten skin test doses of toxin, it was observed that the patient's blood serum revealed the absence of antitoxin. This loss of antitoxin was determined by mixing a definite amount of the patient's blood serum with increasing doses of the toxin. The mixtures were then injected intradermally in susceptible persons. Failure of the patient's blood serum to neutralize ten skin test doses of the erysipelas toxin was taken to indicate loss of immunity to antitoxin.

Careful investigations were made in a group of patients with habitual erysipelas. Some of the patients sustained recurrent attacks regularly every four weeks to three months. Such persons were found to contract the disease almost simultaneously with the reappearance of a positive skin reaction with ten skin test doses of toxin.

It was decided to attempt active immunization with gradually increasing doses of *Streptococcus erysipelatis* toxin. The extensive work done on the Dick method of active immunization against scarlet fever, and, in particular, the logical and comprehensive work on this subject by Young and Orr on the dosage of toxin in scarlet fever immunization, made the parallel work on erysipelas immunization relatively easy. A course of active immunization against recurrent attacks of erysipelas was accomplished by means of biweekly intramuscular injections of 500, 5,000 and 50,000 skin test doses of the extracellular and intracellular toxin produced by the *Streptococcus erysipelatis.* This course of injections produced in the patient's blood serum a rapidly increasing concentration of antitoxin. In certain persons this concentration reached as high as the capacity of the patient's blood serum, being able to neutralize completely more than 1,000 skin test doses of toxin.

Already, sixty-eight patients with definite histories of recurrent attacks of erysipelas have been actively immunized by Birkhaug. Recently, the dosage has been increased by two additional injections of

100,000 and 250,000 skin test doses, respectively. By means of the increased dosage of the toxin it is hoped to prolong the period of active immunization.

It has been most impressive to observe that among these sixty-eight persons who, previous to the course of active immunization, suffered habitual attacks of the disease from every fourth to twelfth week, have, with one exception, been free from subsequent recurrent attacks during a period now exceeding two years.

IMMUNIZATION OF HORSES TO ERYSIPELAS STREPTOCOCCUS TOXIN

In the course of the biologic studies by Birkhaug on *Streptococcus erysipelatis,* which gradually led to the development of the erysipelas streptococcus antitoxin, it became necessary to turn over the manufacture of this antitoxin to a commercial laboratory, in order to supply the professional demand for the erysipelas antitoxin. In 1927, Anderson and Leonard [184] reported comprehensively on the immunization of twenty-one horses by the use of *Streptococcus erysipelatis* toxin alone, by the use of toxin and whole broth cultures containing either dead or living streptococci, or by the Zinsser-Grinnell [185] blood clot method and the injection of filtered or centrifugalized toxin. After numerous experiments, these authors adopted the following method of immunization which yielded the highest titer of erysipelas antitoxin:

The course of active immunization of horses usually began with an initial dose of 50 cc. of *Streptococcus erysipelatis* toxin, each cubic centimeter containing an average of 10,000 skin test doses of toxin. At each subsequent injection, the dose was doubled until the animal showed some unfavorable reaction or until a volume of 300 or 400 cc. of toxin was reached. In the beginning, the injections were made twice a week; this was continued for about three weeks, when the number of injections of toxin was reduced to one a week. Injections were also made by the blood clot method once weekly, and this combination was continued until the animals had been under treatment for approximately three months. At this time trial bleedings were made, and the plasma was tested for antitoxin content. The horses were usually bled from six to seven days after the last injection. The plasma from different horses immunized by this method gave an average test, within three months after immunization, of 5,000 or more neutralizing skin test doses per cubic centimeter. If the general condition of the horse remained good, a gradual increase in the potency of the antitoxin was noted under continued treatment. These authors observed that none of the horses survived as long as the

184. Anderson and Leonard: J. Lab. & Clin. Med. **13**:64, 1927.

185. Zinsser and Grinnell: Proc. Soc. Exper. Biol. & Med. **23**:205, 1925-1926.

animals that were immunized with other toxins, such as diphtheria or tetanus toxin.

The plasma is concentrated by a modification of the Banzhaf method, one similar to that employed for the concentration of diphtheria, tetanus and scarlet fever antitoxins. The average concentration of the plasma has given an antibody concentration of from four to five and a half times. The finished globulin has tested from 40,000 to 70,000 neutralizing skin test doses per cubic centimeter. The erysipelas antitoxin is distributed in doses containing 500,000 or more neutralizing skin test doses.

STANDARDIZATION OF ERYSIPELAS STREPTOCOCCUS ANTITOXIN ON MAN

Extensive studies with streptococcal filtrates have shown that man is the only animal susceptible to the toxins produced by *Streptococcus scarlatinae* and *Streptococcus erysipelatis*. Recent progress in the etiology, specific therapeutics and prevention of scarlet fever and erysipelas is mainly due to experimental data obtained on human volunteers. After reviewing critically the various methods of standardizing streptococcal antitoxins in animals, as well as the in vitro tests, all of which fall short as reliable criteria of standardization of toxin-antitoxin mixtures, Birkhaug [186] suggested, in 1928, a simplified method for the standardization of the erysipelas streptococcus antitoxin in man. After the potency of a standard *Streptococcus erysipelatis* toxin is determined in terms of number of skin test doses contained 1 cc., definite amounts of the toxic filtrate and the unknown erysipelas antitoxic serum are mixed and placed in the icebox for twelve hours, after being gently shaken. After the period in the icebox, the tubes are again shaken to insure proper distribution of the toxin-antitoxin mixture. From each tube 0.1 cc. is removed with a tuberculin syringe, and these amounts are injected separately into the skin on the flexor surface of the forearm, interspaced by a distance of about 5 cm. The person on whom these tests are performed has previously been tested with standard skin test doses of the toxin and shows a typical localized erythema measuring about 1.5 cm. in diameter at the site of injection, in the course of twenty-four hours. The results of the injections of the toxin-antitoxin mixture are read in from twenty to twenty-four hours after inoculation. The area in which the reaction remains negative following the intradermal injection of the largest amount of undiluted toxin mixed with 0.01 cc. of antitoxin is chosen arbitrarily to represent the basis of calculation of the antitoxin unit. At an informal conference in Washington, D. C., in May, 1925, the Scarlet Fever Antitoxin Committee decided that "a unit of scarlet fever antitoxin is the amount of serum which completely neutralizes 100 skin test

186. Birkhaug: J. Infect. Dis. **42**:35, 1928.

doses of *Streptococcus scarlatinae* toxin." For the sake of uniformity this standard of antitoxin measurement has been adopted for *Streptococcus erysipelatis* antitoxin and toxin. In order to insure the highest possible therapeutic benefit to the patients stricken with erysipelas, the department of bacteriology of the University of Rochester School of Medicine and Dentistry has endeavored to require of the various commercial products of the erysipelas antitoxin a content of at least 500 units of antitoxin per cubic centimeter before the antitoxin is released for general distribution.

CONCLUSIONS

I remain deeply impressed by the fact that through the entire history of events associated with the clinical, anatomic, bacteriologic and immunologic studies of erysipelas, there runs an unbroken cord which unites the most ancient medicine with the present enviable state of medical knowledge. After a study of the extensive literature that has accumulated on this subject alone, I firmly believe that it is conducive to precision and clearness to regard *Streptococcus erysipelatis* as the true agent of the infection. The many data, when viewed both pro and con, bear the unmistakable marks of specificity, no longer aprioristic, but based on careful observation and experimentation.

If the generous tribute to this work, offered by Symmers and Lewis, remains henceforth true, that "the antitoxin treatment of erysipelas marks an advance, the results of which are commensurate with those obtained in the treatment of diphtheria and as far as the immediate attack is concerned, erysipelas is now a vanquished disease," then the medical profession should be grateful that a reward has come at last to the large host of investigators who not singly but unitedly made possible the unravelling of the specific facts known today concerning the etiology of erysipelas.

Notes and News

University News, Promotions, Resignations and Appointments.—In Berlin, Otto Lubarsch retired from the professorship of pathology on April 1; Walther Hueck, Leipzig, has been appointed as successor to Professor Lubarsch. George B. Gruber, Innsbruck, has been appointed to the professorship of pathology in Göttingen, made vacant by the retirement of Eduard Kaufmann.

It is reported that Gustav Hauser, professor of pathology in Erlangen, will retire on Oct. 1, 1928, and that Paul Ernst has retired from the professorship of pathology in Heidelberg.

Charles Weiss, assistant professor of bacteriology at the school of tropical medicine of Columbia University and the University of Porto Rico, has been appointed associate professor of experimental bacteriology in the department of ophthalmology at Washington University, St. Louis.

Ernest Carroll Faust, who for the past eight and a half years has been director of the parasitologic laboratory of the Peking Union Medical College, China, has resigned to accept the professorship of parasitology in Tulane University, New Orleans.

In Syracuse University, Robert B. Hartsfield has been made instructor in pathology.

In Yale University, George Valley has been made instructor in general bacteriology; George A. Hunt, instructor in bacteriology and immunology; Douglas H. Sprunt, instructor and resident in pathology; Jarry M. Zimmerman, instructor and assistant resident in pathology; Henry W. Ferris, instructor in pathology, and Marvin C. Scarbrough, lecturer in pathology.

William Charles White, pathologist in charge of research in tuberculosis, U. S. Hygienic Laboratory, and chairman of the medical research committee, National Tuberculosis Association, has been made chairman of the division of medical sciences of the National Research Council for 1928-1929.

In the University of Chicago, Richard H. Jaffé, pathologist to the Cook County Hospital, has been appointed professorial lecturer in pathology.

Fred W. Stewart of the Rockefeller Institute for Medical Research has been made assistant pathologist at the Memorial Hospital and associate in pathology at Cornell University Medical School, New York.

Hans W. Hefke has been appointed fellow in pathology in the Mayo Foundation, Rochester, Minn.

New appointments have been made at the Rockefeller Institute for Medical Research as follows: associates, Robert Hannon, Henry R. Muller, Cornelius P. Rhoads; assistants, Robert B. Corey, Martin H. Dawson, Malcolm Dole, Thomas Francis, Jr., Donald C. Hoffman, Christopher Johnston, Currier McEwen, Norman S. Moore, James F. Pearcy, Albert L. Raymond, Alexander Rothen and Charles A. Slanetz.

American Society of Clinical Pathologists.—Frank W. Hartman is the new president, Charles R. Drake is the vice president, and Harry J. Corper is secretary-treasurer of the American Society of Clinical Pathologists.

Quensel Memorial Number.—Numbers 1 and 2 of volume 34 of *Upsala Läkareförenings Förhandlingar* is dedicated to Ulrik Quensel, professor of pathology in the University of Upsala, in commemoration of his sixty-fifth birthday. The combined number consists of some 600 pages and contains many articles, for the most part in German, of general pathologic interest.

W. M. L. COPLIN, M.D.
1864-1928

Obituary

W. M. L. COPLIN, M.D.

1864-1928

William M. L. Coplin was born near Clarksburg, W. Va., on Nov. 1, 1864. He received his preliminary education in Ohio and graduated from the Jefferson Medical College in 1886. After a year as intern at the Jefferson Hospital, he entered the field of pathology. He became professor of pathology and bacteriology at Vanderbilt University in 1895 and returned to Jefferson Medical College as professor of the same subjects in 1896. In 1905, Dr. Coplin was appointed to fill an unexpired term as director of the Department of Public Health and Charities of Philadelphia. During this period, he had much to do with the organization of the new municipal hospital and was responsible for numerous improvements at the Philadelphia General Hospital.

One of his chief interests during his years at Jefferson Medical College was the organization and equipment of the medical museum. His energetic devotion to this work resulted in a splendid teaching museum, and although many fields of medicine and various forms of hospital activity later claimed his attention, morbid anatomy from a practical teaching standpoint, closely linked to clinical medicine, remained paramount among his many interests.

In May, 1917, Dr. Coplin was selected to take charge of the United States Army Base Hospital, no. 38, and, despite the fact that he was urged not to burden himself with such heavy responsibilities, he entered energetically into the organization of this base hospital and served as its director until Sept. 1, 1918. Later he assumed the duties of director of the laboratory division of the Third Army with headquarters at Coblentz, Germany. He was discharged from the army in April, 1919, with the rank of colonel, and received citation for meritorious service.

Always an exponent of hard work, Dr. Coplin entered into his usual strenuous routine of teaching and hospital activities on his return from Europe. While working in his beloved museum, he was seized with an attack of apoplexy from which he gradually almost completely recovered. He resigned from Jefferson Medical College in 1922 and made his home in Atlantic City where he lived contentedly, frequently enjoying visits from his former associates and students.

Dr. Coplin was pathologist to the Philadelphia General Hospital and to the Jefferson Hospital and was president of the staff of the latter institution. He was a fellow of the College of Physicians of Philadelphia

and of the Association of American Physicians. During his entire career, he was active in the Pathological Society of Philadelphia, often appearing on the program but more frequently inspiring younger men to make presentations. He was a frequent contributor to medical literature and was the author of a manual of pathology which reached a fifth edition.

Dr. Coplin died of angina pectoris on May 29, 1928, and is survived by a widow and two daughters. Jefferson Medical College particularly mourns its loss, for during thirty-five years he gave lavishly of his time and energies to the betterment of that institution. Thousands of students will always be grateful for his devotion to their interests, and indebted, indeed, are those young men who entered clinical medicine through the doors of pathology under his skilful guidance.

EDWARD WEISS.

Abstracts from Current Literature

Pathologic Physiology

EMPTYING OF THE GALL BLADDER IN PREGNANCY. L. R. WHITAKER and W. C. EMERSON, Am. J. Physiol. **84**:516, 1928.

In observations made by means of the x-ray on pregnant cats, the gallbladders of which had been filled experimentally with iodized oil, it was found that when the animals were in good condition, there was normal emptying; the occasional failure of this organ to empty normally in pregnancy may be paralleled in non-pregnant animals. Pregnancy, in itself, does not exert any evident inhibitory effect on this function.

H. E. EGGERS.

EMOTIONAL POLYCYTHEMIA IN RELATION TO SYMPATHETIC AND MEDULLI-ADRENAL ACTION ON THE SPLEEN. J. J. IZQUIERDO and W. B. CANNON, Am. J. Physiol. **84**:545, 1928.

In cats excited by the presence of a dog, there was observed a pronounced rise in the red cell count, averaging 20 per cent in the more moderately reacting animals. When excitement did not occur in the usual way, the polycythemia was absent. The hematocrit and hemoglobin determinations were not proportionally increased; this is explained by the presence of a larger percentage of corpuscles of small size. The reaction failed after removal of the sympathetic nerve strands in the upper part of the abdomen and bilateral cutting of the splanchnic nerves; reaction was not determined by innervation of the liver, as it was absent when the innervation of this organ was left intact and that of the remaining viscera of the upper part of the abdomen abolished. Section of the nerves to the spleen prevented the reaction, unless the excitement was associated with marked struggling. The inactivation of the suprarenal medulla did not have a marked effect.

H. E. EGGERS.

THE INFLUENCE OF THYROIDECTOMY ON THE INDOPHENOL-OXYDASE CONTENT OF ANIMAL TISSUES. J. A. DYE and R. A. WAGGENER, Am. J. Physiol. **85**:1, 1928.

Proceeding on the assumption that the activity of the oxydasic systems and the regulation of gaseous exchange play an important part in maintaining normal metabolism in the body, the writers studied the indophenol-oxydase content of heart, kidney, liver and skeletal muscle of normal and thyroidectomized lambs and pups. In all cases a marked diminution was found in indophenol-oxydase in the thyroidectomized animals.

H. E. EGGERS.

THE INDOPHENOL-OXYDASE CONTENT OF ANIMAL TISSUES AFTER TOTAL THYROPARATHYROIDECTOMY IN DOGS. J. A. DYE and R. A. WAGGENER, Am. J. Physiol. **85**:14, 1928.

In the heart muscle, liver and skeletal muscle of fully grown parathyroidectomized dogs there was found an increased oxidative power as indicated by their ability to oxidize alpha-naphthol and dimethylparaphenylendiamine hydrochloride into indophenol blue. The estimated values varied from organ to organ of the same animal, and from animal to animal, but the increase was indicated in the group values of all these tissues. It was not shown by kidney tissue. The severity of the tetanic seizures was not sufficiently graded to make possible an exact correlation between this symptom and the increase in oxidative power.

H. E. EGGERS.

A Study of the Effect of Yeast on Metabolism. E. U. Still and E. M. Koch, Am. J. Physiol. **85**:33, 1928.

The effects of yeast were determined in persons on controlled diets—first on a low purine and low protein diet then on a high protein, meat-containing diet. The results were as follows: The addition of yeast to the low protein and low purine diet, after the body's elimination of uric acid had reached a low point, did not cause an increase in the elimination of this substance. If it was added while the elimination of uric acid was still actively going on, or if added to a diet high in protein, an increased elimination of uric acid followed promptly. This fell off rapidly when the yeast was discontinued. Several weeks of feeding of yeast did not cause an increase of urea in the blood. Urinary phenols were reduced in five of six persons, possibly as the result of an alteration of intestinal flora with reduced putrefaction. During the ingestion of yeast there was an increase in the total elimination of nitrogen and phosphorus, mostly accomplished through the intestines. Regularity and ease of evacuation were increased by the ingestion of yeast, probably as the result of the greater bulk. There was not any noticeable change in the moisture content of the feces.

H. E. Eggers.

A Study of the Inorganic Constituents of the Body with Respect to Their Stimulating Effect on Sugar Metabolism. W. E. Burge and A. M. Estes, Am. J. Physiol. **85**:103, 1928.

Using goldfish immersed in water containing dextrose, to which known amounts of various inorganic solutes were added, the utilization of sugar by the fish was determined by direct analysis of the water after thirty hours. Of the salts studied, dipotassium phosphate produced the most marked increase in the utilization of sugar. Disodium phosphate caused a small increase, magnesium sulphate caused a diminution, probably by its anesthetic effect, and the other salts were without effect. Since the phosphate of potassium occurs in the solids, and so in the muscles, the place of greatest sugar metabolism, it is assumed that this salt operates by accelerating the utilization of sugar there. It was also found that insulin in small amounts in these conditions caused increased utilization of the sugar, and that large amounts caused convulsions, which abated on removal of the fish to sugar solutions. The utilization of sugar in Paramecium was likewise increased by dipotassium phosphate, and by insulin.

H. E. Eggers.

Sterility in Inbred Rats. H. M. Evans, Am. J. Physiol. **85**:154, 1928.

Attempts at the interbreeding of rats that had been propagated by brother-sister mating for a large number of generations failed in from 62 to 76 per cent of the inbred rats, as compared with 20 per cent of normal stock. When copulation took place, there was not any apparent loss of conceptive power. The indisposition to mate was shown to a greater degree by the male than by the female.

H. E. Eggers.

Effect of Intravenous Injection of Sodium Chloride on the Distribution of White Blood Cells in the Peripheral Circulation. L. A. Beard and J. W. Beard, Am. J. Physiol. **85**:169, 1928.

In eight rabbits which had been previously standardized and which were injected intravenously with from 10 to 15 cc. of a dilute solution of sodium chloride, uniform variations of the peripheral white cell count were observed. The count fell, following the injection, to less than half the normal number, and remained at this low level for from 30 to 50 minutes; it then rose to normal or above. The polymorphonuclear neutrophils were chiefly involved in this fall, and gave corresponding variations in number; the eosinophils behaved similarly, but were too few in number appreciably to affect the total picture; lymphocytes diminished gradually in number; the number of monocytes fell to zero with the beginning of the leukopenia, and remained at zero until after the rabbit's recovery from the leuko-

penia; then monocytes made a gradual reappearance. Changes were not observed in the number of the red blood cells. The changes described are similar to those previously described as following injections of proteins, bacterial products, etc., and the writers believe that this similarity in behavior is to be explained either as having a common physical basis or as due to a common secondary effect.

H. E. EGGERS.

OBSERVATIONS ON THE INTRACAPSULAR PRESSURE AND THE MOLECULAR CONCENTRATION OF THE RENAL CAPSULAR FLUID IN NECTURUS. H. L. WHITE, Am. J. Physiol. **85**:191, 1928.

This article is of pathologic interest, as the writer finds that the molecular concentration of the glomerular fluid in *Necturus* is higher than that of the serum, indicating that the glomerulus in this animal is an actively secreting structure. He considers it probable, however, that the secretory activity is accompanied by a simultaneous filtration.

H. E. EGGERS.

THE EFFECTS OF SELECTIVE SOLAR IRRADIATION ON THE GROWTH AND DEVELOPMENT OF CHICKS. C. SHEARD and G. M. HIGGINS, Am. J. Physiol. **85**:290, 1928.

Young chicks were found to be unaffected, as regards weight, during the first two months of their life, by housing under selective filters which permitted the passage of maximal or minimal ultraviolet irradiation, or maximal or minimal irradiation with the longer wave lengths. During this period, growth was slightly greater if 2 per cent by weight of cod liver oil was added to the diet; this irrespective of their irradiation. At the end of six months, the average weight of chicks fed on standard diet and 2 per cent cod liver oil was practically the same, regardless of the light filter behind which they had been sheltered. Evidently, cod liver oil is able to induce normal growth regardless of the type of irradiation. In chicks which were housed behind blue and amber glass and fed on a diet without cod liver oil, there was a decided decrease in average weight. In such animals there was observed hypertrophy of the parathyroids, which the writers interpret as a compensatory action in the body's effort to promote normal growth; ultimately this is inadequate, and subnormal weight and signs of rickets appear.

H. E. EGGERS.

THE EFFECTS OF SELECTIVE SOLAR IRRADIATION ON THE PARATHYROID GLANDS OF CHICKS. G. M. HIGGINS and C. SHEARD, Am. J. Physiol. **85**:299, 1928.

Chicks fed with a standard diet were grown under various glass shelters which transmitted known portions of the solar spectrum. In those grown under amber and blue glass, enlargement of the parathyroids—a hyperplasia rather than a hypertrophy—was seen within the first few weeks. In chicks fed with 2 per cent by weight of cod liver oil in addition to the standard diet, the changes in the parathyroid were less conspicuous. The hyperplastic changes were shortly followed by retrogression, manifested by breaking down of the central epithelial cell cords, with increased connective tissue here, while at the same time new cells continued to be produced at the periphery. The retrogressive processes were accompanied by the formation of two types of cysts, lined either with columnar epithelium or with layers of flattened cells. Indications of the parathyroid changes were not found in the mineral content of the blood, or in the general activity.

H. E. EGGERS.

SOME PHYSIOLOGICAL EFFECTS OF COPPER. F. B. FLINN, Am. J. Physiol. **85**: 369, 1928.

Copper is normally found throughout the tissues. It is present in largest concentration in the liver, where it appears to become removed from the blood stream

and excreted into the bile. It is not found in the bones except in traces. The oxygen-carrying capacity of the blood is increased when traces of copper are added to the diet. Ingested copper derivatives are not retained in the body except in small amounts.

ARTHUR LOCKE.

ACQUIRED ARTERIOVENOUS FISTULA. W. M. YATER, Ann. Surg. **87**:19, 1928.

In three of four cases of acquired arteriovenous fistula, the oxygen content of blood taken from a vein in the region of the fistula revealed the presence of arterial blood. The author suggests this as a pathognomonic criterion in cases in which there is doubt as to the presence of an arteriovenous anastomosis.

N. ENZER.

THE EFFECT OF ANESTHESIA ON THE RECOVERY PROCESS IN MAMMALIAN SKELETAL MUSCLES. C. N. H. LONG, J. Biol. Chem. **77**:563, 1928.

The restoration of muscle glycogen is almost inhibited during anesthesia.

ARTHUR LOCKE.

A STUDY OF THE POSSIBLE RÔLE OF ALUMINUM COMPOUNDS IN ANIMAL AND PLANT PHYSIOLOGY. E. V. MCCOLLUM, O. S. RASK and J. E. BECKER, J. Biol. Chem. **77**:753, 1928.

Aluminium is not a constituent of animal tissues. Its compounds are not absorbed from the stomach or intestinal tract and do not form a union with the stomach or intestinal walls. They do not appear to have a deleterious action on growth, reproduction or general well being in rats, even when added to the diet in concentrations of as high as 600 parts per million.

ARTHUR LOCKE.

COPPER AND IRON IN NUTRITION. J. WADDELL, C. A. ELVEHJEM, H. STEENBOCK and E. B. HART, J. Biol. Chem. **77**:797 and 813, 1928.

The hemoglobin level in anemic rats was not materially increased by the addition of inorganic iron salts to the diet. Addition of the ash from dried beef liver, dried lettuce and yellow corn, or of acid extracts of the respective ashes, was more effective. The potency of a commercial preparation of liver extract, successfully used for the treatment of pernicious anemia in man, was found to persist in the ashed preparation, in acid extracts of the ash and in sulphide precipitates from the ash extracts. Copper was present in the sulphide precipitates.

ARTHUR LOCKE.

THE BLACKTONGUE-PREVENTIVE ACTION OF SIXTEEN FOODSTUFFS. JOSEPH GOLDBERGER, G. A. WHEELER, R. D. LILLIE and L. M. ROGERS, Pub. Health Rep. **43**:1385, 1928.

The foodstuffs that are sources of the preventive of blacktongue appear also to be good sources of the preventive of pellagra; foodstuffs that are poor sources of, or lack the preventive of, blacktongue likewise appear to be poor sources of, or to lack the preventive of, pellagra. The indications are that experimental blacktongue and pellagra are identical. From the study of prevention of blacktongue in the dog, liver, salmon, and egg yolk are recommended for the prevention of pellagra in man.

LIVER FUNCTION IN SPRUE. S. S. SOKHEY, S. K. GOKHALE, M. A. MALANDKAR and H. S. BILLIMORIA, Indian J. M. Research **15**:553, 1928.

In sprue, the liver is not affected to such an extent as to show impairment in tests of function.

STUDIES ON LATHYRISM. R. MCCARRISON, Indian J. M. Research **15**:797, 1928.

A pure culture of *Lathyrus sativus* (Khesari), one of *Vicia sativa* (akta) and the khesari used by sufferers from lathyrism in Rewah did not cause lathyrism or any disease of the nervous system in rats.

AUTHOR'S SUMMARY.

THE EXPERIMENTAL PRODUCTION OF STONE-IN-THE-BLADDER. R. MCCARRISON, Indian J. M. Research **15**:801, 1928.

Stone in the bladder in rats is due to the insufficiency in the experimental diets of a substance or substances (probably vitamin A) which whole milk of good quality provides in abundance. This substance is not present in sufficient quantity in certain of the vegetable oils (linseed and sesame) in common use in India. Cystitis is not a necessary forerunner of stone in the bladder in rats.

AUTHOR'S SUMMARY.

EXPERIMENTALLY PRODUCED LYMPHADENOID GOITRE. R. MCCARRISON, Indian J. M. Research **15**:909, 1928.

Lymphadenoid goiter, as described by William and Pearse in man, has been produced experimentally in rats. The disease is induced in approximately 25 per cent of these animals by diets containing from 72 to 82 per cent of white flour, from 5 to 15 per cent of vitamin-poor animal protein, 8 per cent of olive oil and 5 per cent of McCollum's saltmixture containing 0.45 per cent of potassium iodide but no manganese. Lymphadenoid goiter is not due to a deficiency of iodine in the food but to an insufficiency of vitamins of the A, B, C and D classes, combined with a deficiency of certain inorganic elements (of which manganese appears to be one) and of "roughage." In man, it may be expected to occur in young and growing persons who subsist on diets composed largely of white flour poor in vitamin and manganese or other vitamin-poor carbohydrate, vitamin-poor protein and vitamin-poor fats, with a paucity, or absence from the diet, of fresh fruit and green leafy vegetables. Such diets, judged by their effect on rats, induce in the thyroid gland a state of physiologic subnormality, which is, as Williamson and Pearse have rightly concluded, the basis of lymphadenoid goiter.

AUTHOR'S SUMMARY.

INFLUENCE OF THE MUSCULATURE ON BLOOD-CONTENTS OF CAPILLARIES. A. JORES, Ztschr. f. d. ges. exper. Med. **59**:172, 1928.

A technic is described for injecting the capillaries of the skeletal muscles and the heart muscle of rabbits. The number and diameter of the capillaries are determined microscopically in sections fixed in formaldehyde. Muscular activity (contraction) causes a compression of capillaries (including precapillary arterioles and venules). In the case of the heart muscle, systolic contraction causes a partial emptying, and diastolic relaxation, a refilling of the capillaries. The effect of the musculature on capillaries is pumplike; reflex or stasis is prevented by arterial pressure on one hand, and by the valves of the vein on the other.

B. LUCKÉ.

EFFECT OF MENSTRUAL CYCLE ON ERYTHROCYTES. L. DETRE, Ztschr. f. d. ges. exper. Med. **59**:240, 1928.

The number of erythrocytes gradually increased during the premenstrual period; a maximum is reached just before the beginning of menstruation; this is followed by a gradual decrease to a minimum in the postmenstrual period. The volume of erythrocytes is greatest in the premenstrual period, and smallest in the postmenstrual period. The hemoglobin content of the erythrocytes varies inversely to this volume. It is suggested that the premenstrual erythrocytosis is dependent on the "premenstrual acidosis" described by a number of observers.

B. LUCKÉ.

EFFECT OF REDUCTION OF ATMOSPHERIC PRESSURE ON THE BLOOD AND THE HEMAPOIETIC ORGANS. J. BALÓ, Ztschr. f. d. ges. exper. Med. **59**:303, 1928.

The experiments were made on rats at Davos (altitude 1,560 meters); atmospheric pressure was diminished by the use of an apparatus previously employed by Laubender (*Biochem. Ztschr.* **165**:425, 1925) and Rosin (*Beitr. z. path. Anat. u. z. allg. Pathol.* **76**:153, 1926). The animals were subjected to a maximal reduction of atmospheric pressure of about 200 millimeters of mercury for seventy-two to eighty hours. An increase was found in the number of erythrocytes proportional to the lowering of the atmospheric pressure (from a normal of about 6,000,000 to from 8,000,000 to 9,000,000). The blood platelets were likewise increased. The total white cell count decreased from a normal range of from 4,800 to 11,000 to a range of from 2,900 to 7,900; this decrease was due to polymorphonuclear leukocytes; a relative lymphocytosis was found. The erythropoietic foci in the bone marrow were enlarged. The megalokaryocytes showed degenerative changes; they were invaded by phagocytic leukocytes. In the pulp cells of the spleen were found extruded nuclei of erythrocytes. Slight fatty changes were observed in the liver. The thyroid and the pituitary appeared unaffected.

B. LUCKÉ.

THE EXPERIMENTAL SUBSTITUTION OF AN OMENTAL ANASTOMOTIC CIRCULATION FOR THE RENAL VEIN. LUDWIG PAUNZ, Ztschr. f. d. ges. exper. Med. **59**: 391, 1928.

The right kidneys of twelve dogs were removed; the left kidneys were decapsulated and split. A portion of the omentum was placed in the wound; the remainder was wrapped around the organ, which was then replaced in its normal position. Six weeks afterward the renal vein was ligated. No infarction occurred. The functional disturbances following ligation (albuminuria, hematuria) were temporary and disappeared within one or two weeks. The urinary output was normal; the variability of kidney function remained unimpaired. There was an abundant collateral circulation through the anastomosed omentum. On histologic examination, the renal tissue was found to be normal. In control animals in which the renal vein was ligated after decapsulation of the kidney, the organ invariably became necrotic.

B. LUCKÉ.

EFFECT OF INACTIVITY ON BONE GROWTH. K. FRIEDLANDER and JOHANNES THIERSE, Ztschr. f. d. ges. exper. Med. **59**:724, 1928.

The study deals with the question of how the development, length, form, structure and chemical composition of bones is affected by inactivity of the musculature during the period of growth. That there is a definite relation between muscular function and the development and structure of bones appears to be an established fact; the authors cite a number of clinical as well as experimental reports in support of this view. In young dogs and rabbits, inactivity of an extremity was produced by section of the nerve, or by immobilization of the part in a cast; the duration of the experiment was from five weeks to six months. The opposite normal extremity served as a control. It was found that the bones of the inactive extremity were lighter, the water content was greater and the ash content (of the dried bones) was less than that of the normal bones. The inactive bones were more slender, and cast a less dense shadow on the x-ray plate; the spongy part was rarified and the cortex was thin. Usually there was an increased curvature. In some cases the bones were longer than the controls; the epiphyseal line of the inactive bones was less broad than in the normal bones (x-ray, histologic examination); this is interpreted as a sign of accelerated growth. All the changes varied directly with the duration of the experiments and the degree of immobilization. Loss of weight of bones, increase in water content and decrease of ash content were observed as early as five or six weeks after immobilization.

B. LUCKÉ.

EFFECT OF EXPERIMENTAL BILE STASIS ON THE HEMOPOIETIC ORGANS OF RABBITS. A. v. TENEY, Ztschr. f. d. ges. exper. Med. **60**:102, 1928.

Ligation of the common bile duct or parenteral injection of bile led to rapid diminution in the number of erythrocytes. This was followed by marked regenerative activity in the bone marrow, and extra medullary hematopoiesis in the spleen, lymph nodes and liver. The blood picture resembled that of pernicious anemia (anisocytosis, poikilocytosis, polychromatophilia, normoblasts, lymphocytosis, high color index, etc.). There was depletion of lympocytes in the lymph nodes and the spleen; this may be related to the lymphocytosis of the peripheral blood. On the other hand, numerous plasma cells were found in the spleen and the lymph nodes. The author suggests that plasma cells may represent a transition stage between lymphocytes and erythroblasts. The animals died in from one to three weeks after operation, from a progressive anemia.

B. LUCKÉ.

THE STERILITY OF WHITE RATS ON CERTAIN SYNTHETIC DIETS. U. SUZUKI, W. NAKAHARA and N. HASHIMOTO, Japan M. World **8**:31, 1928.

White rats were fed on a synthetic diet practically free from fat and lipoid, but adequate for the growth. Prolonged observations proved that reproduction did not take place among the rats on this diet, though their general nutrition was good. It was found that the sex glands of the male rats were markedly degenerated, and microscopic examination revealed almost no spermatozoa. Small amounts of cholesterol or of synthetic triolein added to the diet did not change the matter; the rats remained sterile. Nor did daily exposure of the rats to ultraviolet light produce any effect in this respect. Since these diets were not deficient in any other known factor, the reproductive failure may be attributed to the absence of the so-called vitamin E.

AUTHORS' SUMMARY.

Pathologic Anatomy

PRIMITIVE HUMAN HEARTS (COR BILOCULARE AND TRILOCULARE). R. HUGH WOOD and GEORGE A. WILLIAMS, Am. J. M. Sc. **175**:242, 1928.

Two cases of functionally bilocular human hearts are described. In one of them, that of a girl who lived to the age of 15, the heart consisted of one atrium and one ventricle, in each of which evidence of abortive septum formation was found. The heart of the other patient consisted of a single ventricle and a large right atrium, which was only partially separated from the rudimentary left atrium. Other congenital abnormalities were present in both cases. A review of the literature revealed much confusion as to the classification of congenital defects of the heart. Such terms as "single heart" and "cor biloculare" are misnomers, for every animal with a separate pulmonary circulation must have present in some degree the anlagen of a double heart.

S. D. SIMON.

A STUDY OF THE HISTOPATHOLOGY OF THE SO-CALLED ADENOSARCOMA OF SWINE. WILLIAM H. FELDMAN, Am. J. Path. **4**:125, 1928.

A review of the literature indicates that these tumors have received but scant attention from the standpoint of comparative pathology. Eleven embryonal tumors of swine are described, nine of which had their origin in the kidney and two posterior to this organ in the sublumbar region. A comparison of the specimens from swine with the embryonal renal tumors of the child indicates that the process is comparable in the two species, and that sufficient similarity exists to justify the assumption that there is a common histogenesis. The two tumors in the sublumbar region possibly owed their origin to the failure of certain portions of the mesonephros to be used in the development of the permanent kidney. The embryonal renal tumors of swine, like those of the child, constitute a heterogeneous group. Grossly, it is difficult if not impossible to separate them, but histologically,

two, or perhaps three, types exist. They fall under the following headings: embryonal adenocarcinoma, embryonal adenosarcoma and embryonal fibrosarcoma. A pure embryonal fibrosarcoma of the kidney of swine has not as yet been described. Available data indicate that this group of tumors constitute the most common neoplasm of swine, a species which seems to possess a relative lack of susceptibility to tumorous proliferations. Unlike the closely related group of tumors of the child, those of swine do not appear to embarrass the health. Perhaps this is due in part to the relatively early age at which most swine are slaughtered.

AUTHOR'S SUMMARY.

LEIOMYOSARCOMA OF THE SPLEEN IN A BOVINE. WILLIAM H. FELDMAN, Am. J. Path. **4**:139, 1928.

From a review of the literature pertaining to splenic neoplasms in man and the lower animals, it is apparent that such tumors are seldom seen. In this review of primary splenic tumors, fibroblastoma, lymphoblastoma and endothelioma were the varieties encountered. Although the histologic elements for such a tumor are present in the spleen, no case of primary leiomyoblastoma of this organ has been previously described, so far as can be determined from the literature that was reviewed. A case of primary leiomyosarcoma of the spleen of a cow with extensive multiple metastasis to the liver is reported.

AUTHOR'S SUMMARY.

OBSERVATIONS ON THE HISTOLOGY OF THE TUMORS OF THE NERVUS ACUSTICUS. C. P. RHOADS and W. P. VAN WAGENEN, Am. J. Path. **4**:145, 1928.

The type cell of the solitary tumor of the acoustic nerve, the so-called acoustic neuroma, forms collagen, elastic and fibroglia fibrils, also reticulum. The histologic characteristics of the tumor are consistent with those of new growths derived from connective tissue. The development of the characteristic fibrils is not so well marked as in connective tissue growing in other tumors.

The solitary tumor of the eighth cerebral nerve, the so-called acoustic neuroma, should be classed as a perineural fibroblastoma.

AUTHORS' SUMMARY.

INFLAMMATORY BASIS FOR CORONARY THROMBOSIS. ADAM N. BOYD, Am. J. Path. **4**:159, 1928.

Two cases of thrombosis of the left coronary artery are reported. An acute inflammation of the atheromatous plaques appears to have been the immediate cause of the deposition of thrombus. An extensive suppurative process in a person with arteriosclerosis may cause an acute exacerbation of the vascular lesions wherever they are situated, and in the case of the coronaries may lead to a fatal thrombosis.

AUTHOR'S SUMMARY.

SOME OBSERVATIONS ON INCUBATED LEUKEMIC BLOODS. FREDERIC PARKER and C. P. RHOADS, Am. J. Path. **4**:167, 1928.

Blood from myelogenous and lymphatic leukemia was incubated at 37.5 C. as partly clotted blood and in various dilutions. The cells were studied at varying periods. In some instances, two types of cells appeared that are not seen in the blood ordinarily. The origin of these cells remains undetermined. It is suggested that the method used may be of value in the study of normal and other cells in the blood.

CARCINOIDS (ARGENTAFFIN-CELL TUMORS) AND NERVE HYPERPLASIA OF THE APPENDICULAR MUCOSA. P. MASSON, Am. J. Path. **4**:181, 1928.

The axial region of completely obliterated appendexes often (86 per cent of the specimens) contains nerves and neuromas enclosed by a discontinuous sheath

formed by vestiges of the muscularis mucosae. These neuromas always contain argentaffin cells of divers forms. If the argentaffin cells disappear, the neuromas regress and are absorbed individually, notwithstanding their connections with Meissner's plexus of the submucosa. Study of partially obliterated appendexes shows that these neuromas arise from the periglandular plexus and that they often continue the neuromatous evolution which had commenced when the mucosa still contained gland tubules. This periglandular and subglandular neuromatosis always occurs in nerves inhabited by argentaffin cells. The intranervous argentaffin cells spring from the epithelium that lines the bottom of the glands of Lieberkühn. Reversing the order in which these observations were made suffices to reconstitute the probable and logical chronological order of the phenomena. Certain intestinal cells bud out and migrate into the nerves. Here they become argentaffin. They differentiate into various forms, cylindrical cells grouped in rosettes or vesicles, cells of ganglion type, of Schwannian type and neurocrine cells. The nerves containing them grow and become neuromas, or disappear if the cells themselves disappear. Carcinoids result from the autonomous proliferation of the isolated neurocrine cells present in the neuromas. In short, by its neuromas and by the argentaffin cells which determine their growth and which are linked with their persistence, the periglandular plexus of the appendix exhibits a remarkable autonomy.

THE PATHOLOGIC ANATOMY OF TULAREMIA IN MAN. ERNEST W. GOODPASTURE and S. JOHN HOUSE, Am. J. Path. **4**:213, 1928.

The diagnosis of this case rests finally on the history, clinical course, pathologic anatomy and a positive agglutinin test. Rapidly following a scratch on the right index finger, received while dressing wild rabbits, a local ulcer developed. The ulcer expanded slowly and its base became lined by necrotic tissue. There was a relatively slight inflammation about it. The subsequent involvement of the lymph node is directly attributable to the lesion on the finger. First, the right axillary nodes became enlarged and painful. There was a progressive infection of lymph nodes extending from the right axilla to the mediastinum, downward along the esophagus through the diaphragm and across the lesser curvature of the stomach into the nodes of the hilum of the liver. Microscopically, the ulcer of the finger presents the same type of necrotizing injury and cellular reaction that is found in the lymph nodes, that is, a cellular reaction consisting of polymorphonuclear leukocytes and epithelioid cells aggregated in masses often in a meshwork of fibrin. The focus undergoes a caseating necrosis. The necrosis is surrounded by a marginal zone of epithelioid cells. Many of the foci in lymph nodes begin within lymphatic spaces, others seem to arise within the parenchyma. The entire node becomes acutely inflamed. Blood vessels are dilated. The tissue is edematous and the lymph sinuses are distended with fluid containing numerous cells, large phagocytes, lymphocytes and polymorphonuclear leukocytes intermingling. The larger phagocytes often contain other cells within their cytoplasm. Thus the infection may obviously spread along lymphatic channels. Through these channels, the virus may enter the blood sream, or the blood stream may be entered directly. Frequently one sees in sections of the lymph nodes an area of necrosis encroaching on a blood vessel which becomes thrombosed. Sometimes necrotic blood vessels are seen in the center of a focus of necrosis. The bacteria circulate in the blood at intervals if not continuously, and this is made manifest by the occurrence of typical foci of necrosis in the spleen and liver. Grossly, the appearance of the spleen seems characteristic. It is enlarged, distended with blood, and is speckled on the cut surface with opaque yellowish or chalky areas measuring up to about 1 cm. in diameter, sharply circumscribed, irregular in outline and even with the surface. The larger areas have softened centers. Clinically, the right axillary nodes diminished appreciably in size during the course of the disease, and histologically, the general exudative reaction is less marked and the foci of necrosis appear older, that is, more compact and caseous, than in the lesions elsewhere. The serum removed on the thirteenth day of the disease was reported as agglutinating *Bacterium tularense* in one laboratory and was negative in another.

STUDIES ON LIPOCHROMES: THE IDENTIFICATION OF CAROTIN, XANTHOPHYLL AND ASSOCIATED LIPOIDS IN TISSUES. CHARLES L. CONNOR, Am. J. Path. **4**:235, 1928.

By the use of the usual fat stains on frozen sections of carrots, suprarenal gland, corpus luteum and chicken skin after treatment with fat solvents and other reagents, and on tissues removed from animals after injection of cholesterol, cholesterol esters, fatty acids, soap and lecithin, and by the use of other reagents which might be expected to distinguish lipochromes from other substances in tissues, an effort was made to differentiate carotin, xanthophyll, cholesterol and other lipoids from one another. This has not been entirely successful, but the results justify the following conclusions: Carotin and xanthophyll, the two common lipochromes, do not stain by any of the fat stains ordinarily employed to differentiate them. When associated with a lipoid which does stain, this lipoid takes a blue stain with Nile blue sulphate, and may therefore be cholesterol, cholesterol ester, soap, fatty acid or lecithin. Because the substance with which the lipochrome is associated is usually anisotropic, and carotin and xanthophyll are not, this substance is assumed to be cholesterol or an ester of cholesterol. When a pigment is present in tissues associated with a substance which takes a specific stain for fat, this pigment may be assumed to be a lipochrome, but this is not invariably so. Yellow pigment which tends to coalesce when treated with weak alcoholic potash and formaldehyde, or which crystallizes in the tissue after such treatment, is probably lipochrome. Pigment which disappears or loses its color after treatment with a strong solution of ferric chloride (or other oxidizing agent), if not continued over too long a time, may be assumed to be lipochrome. Pigment which is soluble in the usual fat solvents (ether, petroleum ether, chloroform, etc.) is probably lipochrome, but this treatment must be prolonged and used after dehydration of the tissue with alcohol or acetone to be effective and of differential value. Nile blue sulphate differentiates only neutral fats from all other lipoids, neutral fat staining red, and all other lipoids staining blue. Lecithin, which takes a somewhat lighter stain than the other blue-staining lipoids, may possibly be differentiated from them but careful timing of the staining process is necessary.

AUTHOR'S SUMMARY.

ANGIOMA RACEMOSUM VENOSUM OF THE BRAIN. RICHARD C. BUCKLEY, Am. J. Path. **4**:245, 1928.

The lesion described is considered to be a congenital anomaly of the vascular system although it is named angioma racemosum venosum. Because of the variations in nomenclature and the absence of verification by histologic methods, difficulty has been experienced in selecting cases from the literature. There are but three recorded instances of angioma racemosum venosum which were verified by histologic study. Thirteen reported cases seen at operation and one at necropsy presented the typical gross appearance of this type of vascular abnormality—a collection of nonpulsating, tortuous, thin-walled vessels distended with dark blue blood—but no microscopic examination was made. Another example of the rarity of the lesion is the fact that among 1,500 verified cases of intracranial tumors, Dr. Harvey Cushing has seen at operation only five examples of angioma racemosum venosum and in none of these cases was it possible to remove tissue for histologic study. The lesion has not been diagnosed clinically. It has been usually seen at exploratory cranial operations and recognized by the previously mentioned characteristics. In the several cases examined at necropsy there has been noted a wedgeshaped collection of veins of various caliber which projected into the cerebral tissue for a varying distance from the superficial collection of veins. The histologic studies in the three reported cases showed changes in the vessel walls similar to those described in this report. No previous report has been found of rupture of a vein of an angioma racemosum venosum into the brain or ventricle with subsequent hemorrhage and death.

AUTHOR'S SUMMARY.

SPONTANEOUS RUPTURE OF THE HEART. RICHARD C. BUCKLEY, Am. J. Path. **4**:249, 1928.

The cases reported here present several interesting features. Cases 1 and 3 have associated diabetes mellitus and evidence of infection of the cardiovascular system. The etiology of the infection is not clear in either case. The anterior descending branch of the left coronary artery is completely occluded in each case, and in case 1 the descending branch of the right coronary artery is also occluded. Evidence of old and recent infection of these vessels is presented. Case 1 is of further interest in that the patient was only 35 years old.

THE EFFECT OF THE ORAL ADMINISTRATION OF POTASSIUM IODIDE AND THYROID SUBSTANCE ON THE MITOTIC PROLIFERATION AND STRUCTURE OF ACINI IN THE THYROID GLAND IN GUINEA-PIGS. S. H. GRAY and LEO LOEB, Am. J. Path. **4**:257, 1928.

Oral administration of iodine to guinea-pigs markedly increases the mitotic activity in the thyroid gland during the first three to four weeks. This first phase of increased activity is followed by a second phase of depression, which is accompanied by definite structural alterations in the thyroid gland. We find indications that this second phase is at least partly due to pressure exerted by the contents on the walls of the acini. In contradistinction to the effect of potassium iodide, administration of thyroid gland substance is not followed by a phase of stimulation, but in this case, within the first two weeks, a period of depression sets in which may be accompanied by certain structural changes in the gland. As the result of thyroid feeding, the mitotic activity is diminished as compared with that found in the controls.

AUTHORS' SUMMARY.

OBSERVATIONS ON INCUBATED NORMAL BLOOD. C. P. RHOADS and F. PARKER, JR., Am. J. Path. **4**:271, 1928.

The large phagocytic cells developing in incubated rabbit and human blood may be derived from two sources. These large cells show certain differences in morphology, in staining and in activity for a time which makes it possible to group them in two classes. One group arises from a primitive pluripotential cell normally present though unrecognizable in the blood stream. The second group develops from the blood monocyte.

AUTHORS' SUMMARY.

ERYTHROCYTE SEDIMENTATION IN PSYCHIATRY. JACOB GOLDWYN, Arch. Neurol. & Psychiat. **19**:110, 1928.

The sedimentation reaction of the erythrocytes is a reliable and efficient detector of many somatic disorders and, therefore, is of practical value in psychiatric work. The author concluded that the acceleration of the sedimentation reaction varies directly with the amount of mental deterioration, the amount of organic destruction and the amount of toxicity present. Increased readings are found in all cases of senile psychosis, psychoses due to cerebral arteriosclerosis, general paralysis, neurosyphilis, psychoses showing mental deficiency or somatic disease and acute types of alcoholic psychoses, and in many cases of epileptic psychoses and involutional melancholia. In usual cases of dementia praecox there is a tendency to normal readings while in those complicated by some physical disorder there is a marked increase in the readings. The normal reading in males is up to 6 per cent and in females up to 11 per cent. Readings above these figures are said to be increased.

T. T. STONE.

ENCEPHALITIS PERIAXIALIS CONCENTRICA. JOSEPH BALÓ, Arch. Neurol. & Psychiat. **19**:242, 1928.

A case is reported of encephalitis periaxialis concentrica in a man, aged 23, a law student, who became ill with aphasia, agraphia followed by weakness of

the lower branch of the facial nerve and the disappearance of cremasteric reflexes on the right side. Later, a hemiplegia developed on the right side, with incontinence of the urine and the feces. After death, foci were found in the white matter of the brain varying in size from that of a lentil to that of a pigeon egg. Some foci resembled gray softening; others were characterized by concentric layers composed of normal white matter alternating with layers of gray softening. Fatty degeneration of the medullary sheaths was found in the areas of gray softening. Glycogenic granule cells engulfed the fat droplets. Proliferation of the neuroglia followed degeneration of the medullary sheaths. The formation of giant glia cells was the most characteristic alteration of the neuroglia. Near the foci, the periadventitial lymphatic spaces were filled with products of degeneration, such as granule cells, lymphocytes and plasma cells. Hyaline thickening of the arterial coats were found in widely distant areas of the brain. A general review of the literature is given, with a discussion of the etiology of the condition.

T. T. STONE.

THE THALAMIC AND PARKINSONIAN TYPES OF INFUNDIBULAR TUMORS. L. VAN BOGAERT, Arch. Neurol. & Psychiat. **19**:377, 1928.

In two cases of suprapituitary tumor, symptoms of the thalamo-infundibular syndrome were associated with signs of the extrapyramidal syndrome. The thalamic symptoms were pains of central type, hyperesthesia to cold and trophic changes in the extremities. The infundibular symptoms were polyuria, disorder of glycoregulation and crises of narcolepsy with onirism, fabulation and retrograde amnesia. The extrapyramidal syndrome was represented by slowness, retropulsion and tremor. The thalamic syndrome must be referred to destruction of the internal nucleus of the thalamus — the true Parkinsonian syndrome, to a lesion of the pallidum. The author believes that some of the extrapyramidal disturbance must be attributed to functional troubles in the frontal pole as the result of dilatation of the lateral ventricles from neoplastic extension. In the first case, there was a large tumor of the adamantinoma type which had invaded the tuberian floor, filled the cavity of the third ventricle and pushed the thalamic masses aside laterally; it had invaded the lateral ventricles, which it distended greatly, and had pushed aside the white substance of the frontal pole and the central gray nuclei. Histologically, the pallidum showed marked lesions; the pituitary gland was intact. In the second case, the presence of a tumor above the pituitary body was established by roentgen-ray examination.

T. T. STONE.

PINEAL TUMORS. G. HORRAX and P. BAILEY, Arch. Neurol. & Psychiat. **19**:394, 1928.

In a boy, aged 9 years, a large tumor extending from the splenium of the corpus collosum to the calamus scriptorius was found at necropsy. The tumor probably arose from the pineal body, no trace of which could be seen. A slight degree of macrogenitosomia praecox was present. The tumor was a pinealoma which contained cartilage cells. In a boy, aged 6 years, necropsy revealed a solid tumor 4 cm. in diameter. This occupied the third ventricle and was attached in the infundibular region. The tumor, which was associated with macrogenitosomia praecox, was classified as a ganglioneuroma. In a man, aged 40, a small, flattened, circumscribed tumor of the pineal body was found at necropsy. This was also classified as a typical ganglioneuroma. The authors were unable to interpret the pineal changes as a causal factor in macrogenitosomia praecox.

T. T. STONE.

MALIGNANT CHORDOMA OF THE LUMBAR REGION. C. DAVISON and A. WEIL, Arch. Neurol. & Psychiat. **19**:415, 1928.

The malignant chordoma at the third lumbar vertebra described by the authors is the second, of fifty-eight recorded tumors of this type, situated in the lumbar

region. It differed histologically from the classic chordoma by its more fibrous consistency, and by the mixed character of the cytologic picture. The roentgenogram disclosed sclerosis of the left half of the body of the third lumbar vertebra.

T. T. STONE.

CHOLESTEATOMA OF THE BRAIN. FRANK A. KAY and GEORGE T. PACK, Arch. Neurol. & Psychiat. **19**:446, 1928.

A report is given of an unusually large, epidermoid cholesteatoma, which did not contain hair, originating from the pia mater at the cerebellopontile junction.

AUTHORS' SUMMARY.

ADDISON'S DISEASE WITHOUT PIGMENTATION. D. G. CHRIST and L. G. ROWNTREE, Endocrinology **11**:589, 1927.

A case of typical Addison's disease, except for the absence of pigmentation, is reported. The fatal course was rapid. After death, tuberculosis of the suprarenals was found.

SPONTANEOUS RUPTURE OF THE INTESTINE IN THE NEWBORN. THOMAS H. RUSSELL, J. A. M. A. **90**:1431, 1928.

A careful search of the literature reveals twenty-two cases of rupture of the intestine in the new-born, which, with the case reported here, makes twenty-three now on record. In five cases the rupture occurred during intra-uterine life; in fourteen during birth, and in four during or soon after birth as a complication of imperforate anus or rectum. This condition should be recognized as a clinical entity. The symptoms are characteristic enough to allow of a diagnosis. An early operation should offer a fair prognosis.

AUTHOR'S SUMMARY.

PRENATAL RUPTURE OF THE INTESTINE WITH SUBSEQUENT DYSTOCIA. JAMES HUBERT SKILES, J. A. M. A. **90**:1618, 1928.

The small intestine presented a volvulus. In the twisted loop there was evidence of a healed perforation which had resulted in aseptic peritonitis with an exudate stained with meconium.

ESSENTIAL LIPOID HISTIOCYTOSIS (TYPE NIEMANN-PICK): A CONGENITAL DISTURBANCE IN LIPOID METABOLISM IN INFANTS ASSOCIATED WITH A SPLENOHEPATOMEGALY. ARTHUR F. ABT and WILLIAM BLOOM, J. A. M. A. **90**:2076, 1928.

Anatomically, the disease presents such a distinctive picture that it should not be confused with any other condition. It is characterized in the gross by an extremely enlarged liver and spleen. Both of these organs may extend to the iliac crests, and at autopsy, when the abdomen is first opened, are seen to fill this cavity almost completely. The spleen is of a peculiar salmon-pink color, and on section is homogeneous, save for a scattered mottling with grayish rounded areas 1 mm. in diameter. These are usually surrounded by a thin red zone. The liver is distinctly yellowish and closely resembles that seen in the alimentary intoxications of infancy and in phosphorus poisoning. The suprarenals are enlarged. There seems to be much lipoid in both medulla and cortex. The lungs show a light yellowish mottling, particularly beneath the pleura and following the septums; there is, however, no definite consolidation. The peripheral lymph nodes may or may not be enlarged; those of the body cavities usually are somewhat larger than normal. Microscopically, the spleen, thymus and liver are distorted by the presence of huge numbers of vacuolated foam cells. Most of the lymph nodes and the medulla of the suprarenal also contain many foam cells. These may also be present in surprising numbers in the alveolar walls and spaces of

the lungs. In the liver the foam cells in the blood sinuses can only with difficulty, and by the use of certain stains, be differentiated from the vacuolated liver cells. With hematoxylin and eosin it is frequently very difficult to delineate the foam cells in the liver. With the use of Mallory's aniline blue, however, the foam cells become quite conspicuous in all the organs in which they occur. With this method they stain characteristically bluish gray, and their vacuolated cytoplasm is quite conspicuous against the remainder of the section. Foam cells may also be found freely within the blood vessels of the lungs, the heart, the kidney and the pancreas.

The most striking appearance anatomically is obtained with the use of the stains for the complex lipoids. With sudan III the cells stain a pale orange which is not of sufficient intensity to be considered a positive fat reaction. After mordanting in potassium bichromate, followed by the application of sudan III or Nile blue, or by the method of Lorraine-Smith-Diedtrich, the lipoids are easily demonstrated in practically all the cells and tissues of the body. They are, however, most prominent in the cells of the connective tissue; that is, the reticulum cells of the spleen, bone marrow, lymph nodes and thymus; in the medulla of the suprarenal; in the cells lining the vascular spaces of the liver, and frequently in the lumen of the alveolar spaces of the lung. The postive lipoid reaction is also given by the heart and striped muscle cells, by the epithelial cells of the liver, kidney and thyroid, and by many ganglion cells. Anatomically, the only conditions from which this disease must be different are: (1) Gaucher's disease, in which the large cells have a characteristic morphology with Mallory's aniline blue, and are limited to the spleen, liver, lymph node and bone marrow (Mandlebaum and Downey, Pick and Bloom), and (2) the changes which are observed in certain cases of diabetic coma with lipemia.

In the latter condition there may be a large accumulation of foam cells in the spleen, and to a much lesser extent in the lymph nodes and liver, but there is nothing in this condition comparable to the extensive changes which are described as occurring through the body in lipoid histiocytosis (Niemann-Pick's disease). As Siegmund, Bloom and Kern, Brahm and Pick, Corcan, Oberling and Dienst, and Berman have shown by chemical analysis of the spleen, the stored material in Niemann-Pick's disease is phosphatide. These observations are in close agreement with those recorded on microchemical-histologic examination of the tissues.

COMPENSATORY HYPERTROPHY OF THE LUNG AFTER UNILATERAL PNEUMECTOMY. T. ADDIS, J. Exper. Med. **47**:51, 1928.

In the albino rat, removal of the left lung, which constitutes about one third of the total lung tissue, was followed by an average increase of more than 40 per cent in the mass of the remaining lung, as estimated from the nitrogen content of the almost blood-free tissue.

AUTHOR'S SUMMARY.

ADENOFIBROMA AND FIBRO-ADENOMA OF THE FEMALE BREAST. JOSEPH MCFARLAND, Surg. Gynec. Obst. **45**:729, 1927.

1. Two hundred and eighty-nine growths, supposed to be benign fibro-epithelial tumors of the female breast, were studied clinically and pathologically, for the purpose of harmonizing and simplifying the nomenclature.

2. One hundred and five of them, described under no less than thirty-three different names, were found to be periductal fibromas.

3. One hundred and forty-seven described under much the same names, did not show any histologic indication of being tumors, or of being in any way related to them, but were simply mammary gland tissue, either normal or in some condition of involution.

4. A system of nomenclature that permits tumors and nontumors to be given the same names is too faulty to be continued.

5. As all the tumors resolved themselves into varieties of a single well characterized genus, it would be well to call them all by the same name, and that recommended as most appropriate is Warren's choice, periductal fibroma.

6. In all but thirty-seven cases difficulty was not encountered in separating the tumors from the nontumors.

7. The research having been conducted on material collected from five large, first-class hospitals, where it had been studied by many different pathologists, may be regarded as fairly representative of pathologic tissue work as it is commonly conducted in hospitals.

8. The mistake of calling nontumor tissues by names belonging to tumors may have been the result of overzealousness on the part of the pathologists to cooperate amicably with the surgeons.

9. There are anatomic and physiologic mammary disturbances of the breast that may occasion "lumps" which do not have any relation to tumors, and the surgeons should be so informed and not led to believe that they have removed tumors when none existed.

10. Pathology must remain confused both in theory and in application unless its terminology is so relieved of ambiguity as to be easily understood.

AUTHOR'S SUMMARY.

A CASE OF NERVOUS CRETINISM WITH HISTOLOGICAL EXAMINATION OF THE ORGANS. ELIZABETH COWPER EAVES and MARGARET MARY CROLL, J. Path. & Bact. **31**:163, 1928.

A case of cretinism is described in a girl, aged 15, who died of bronchopneumonia due to aspiration of food. She could neither talk nor walk and was not intelligent. She slept the greater part of the day. At autopsy, a small piece of tissue, 2 Gm. in weight, found in the position of the thyroid, consisted of fibrous tissue, muscle and cartilage; no parathyroid glands were found. The suprarenal glands were somewhat large in proportion to the body weight. Histologically, they were normal. The pancreas was of about normal size and the amount of islet tissue was moderately increased (3.54 per cent). The pituitary gland, weighing 0.24 Gm., was too small for the girl's age, but was within normal limits for the body weight. The posterior lobe was small. Histologically, few eosinophils were found in anterior lobe and there was considerable colloid, some of the masses having concentric rings. The picture gave the impression of an exhausted gland. The thymus gland was large but no definite Hassall's corpuscles were seen. The ovaries were large, but showed fairly normal histologic structure. Mature graafian follicles were not observed. The bones showed large amounts of unchanged cartilage.

The brain weighed 1,035 Gm. and showed narrowing of the convolutions in the parietal and occipital regions. Many nerve cells showed chromatolysis and accumulation of fatty granules in them. No typical large Betz cells could be found in the rolandic area. The neuroglia was increased in many areas.

E. M. HALL.

HYPERCHOLESTEROLEMIC SPLENOMEGALY. S. C. DYKE, J. Path. & Bact. **31**: 173, 1928.

The author describes an interesting case exhibiting a syndrome constituted by subacute pancreatitis, hypertrophic biliary cirrhoses of the liver, icterus, hypercholesterolemia, xanthoma and splenomegaly. The pancreatitis is of importance only in causing partial obstruction to the passage of bile resulting in icterus and cholesterolemia. The latter reached the high mark of 1,250 mg. per hundred cubic centimeters. The xanthomas were, no doubt, the result of the marked

cholesterolemia. Splenomegaly was due to a hyperplasia of large mononuclear cells of reticulo-endothelial origin which were, no doubt, the result of the high cholesterol content of the blood, although inclusions were not found in these cells.

E. M. HALL.

CAUSES AND SEQUENCES IN NEPHRITIS. JOHN GRAY, J. Path. & Bact. **31**:191, 1928.

The evidence for a bacteriotoxic origin for acute nephritis is strong, though it falls short of absolute proof. Clinical investigation and postmortem evidence agree in showing that some variety of streptococcus is the organism most commonly associated with acute nephritis. Bacterial multiplication in the kidneys is not a feature of nonsupprative nephritis, except probably in acute interstitial nephritis. In the other varieties ("glomerular," "glomerulo-tubular" and "tubular"), the bacterial factor is proved by lysis of organisms trapped in the glomeruli with consequent release of endotoxin (Ophüls). Experimental nephritis produced by simple crystalloid chemical substances is always tubular with minimal dosage, and this distribution is explicable on the basis of the "modern" theory of renal function. Alleged "glomerular" crystalloid poisons are really primarily tubular in incidence. Toxins, being colloids, are not filtered through the healthy glomerular tuft, and so are concentrated in the glomeruli by withdrawal of fluid in the filtrate. Hence the nephritis produced by them is initially glomerular. The successive stages in acute nephritis might be outlined in a classification such as the following: *A*. Ordinary type (bacteriotoxic): Concentration of circulating exotoxin (often streptococcal) in the glomeruli (simultaneously, sometimes, bacterial "embolism" in the glomeruli, with lysis and local release of endotoxin)—endoglomerular nephritis. Continuation of the foregoing description, but embolic factor and consequently endotoxic factor soon drops out—epiglomerular and endoglomerular nephritis. Glomeruli become toxin—permeable and albumin-permeable; commencing concentration of toxin in tubules—glomerular-tubular nephritis. Further increase of hyperpermeability of glomeruli; hence further increase in tubular concentration of toxin, and coincident decrease of special concentration of toxin in the glomeruli—mainly tubular nephritis. *B*. Acute interstitial nephritis. Nephritis with a more prominent bacterial factor than the foregoing type, and showing some multiplication of organisms within the kidneys. *C*. Acute suppurative nephritis. Theoretical considerations would of themselves place streptococci as among the organisms most likely to cause ordinary nonsuppurative nephritis frequently, if the foregoing scheme were correct.

AUTHOR'S SUMMARY.

EXPERIMENTAL PRODUCTION OF METAPLASIA AND HYPERPLASIA IN THE SEROSAL ENDOTHELIUM, AND OF HYPERPLASIA IN THE ALVEOLAR EPITHELIUM OF THE LUNG OF THE RABBIT. J. S. YOUNG, J. Path. & Bact. **31**: 265, 1928.

Extensive and varied metaplasia of the serosal endothelium of the visceral pleura, and hyperplasia of the pulmonary epithelium can be produced by injecting into the pleural sac a mixture of sudan III and sodium cholate in olive oil. Sudan III in olive oil is relatively ineffective, and scharlach R has given negative results (with one exception) even with the addition of sodium cholate. The effects of adding sodium cholate are discussed in the light of experimental results, and the biologic dissimilarity of fat-soluble dyes, closely allied in their chemical constitution, is emphasized.

AUTHOR'S SUMMARY.

THE ETIOLOGY OF HEPATO-LENTICULAR DEGENERATION: EXPERIMENTAL LIVER CIRRHOSIS; POISONING WITH MANGANESE, CHLOROFORM, PHENYLHYDRAZINE, BILE AND GUANDIN. E. W. HURST and PHYLLIS E. HURST, J. Path. & Bact. **31**:303, 1928.

The authors attempted to produce cirrhosis in guinea-pigs and rabbits by the use of various agents such as manganese, chloroform, phenylhydrazine, bile and

guanidine. They obtained an extensive peripheral cirrhosis of the liver by the use of manganese. The effect was greatly enhanced by repeated intravenous injections of living *Bacillus coli*. Cirrhosis was not obtained by the other agents. None of these poisons produced degenerative changes in the nervous system. Evidence was not obtained of any connection between cirrhosis of the liver and cerebral changes which might throw light on hepatolenticular degeneration.

E. M. HALL.

PELLAGRA-LIKE LESIONS ASSOCIATED WITH DEFICIENCY OF VITAMIN B_2 IN THE RAT. G. MARSHALL FINDLAY, J. Path. & Bact. **31**:353, 1928.

Rats fed on diets lacking vitamins B_1 exhibit a failure of growth, loss of appetite and decreased body temperature similar to that occurring in rats fed on diet lacking vitamin B. Death occurs in about five weeks, frequently with symptoms of polyneuritis. Histologically, the changes are those associated with inanition. Rats fed on diets lacking vitamin B_2 show failure of growth and as a terminal phenomena loss of appetite and fall in body temperature. Nervous symptoms are absent, but after from eight to ten weeks on the deficient diet lesions of the skin, buccal mucous membrane and tongue develop which are similar to those of pellagra in man. Death occurs in from two to three weeks after the onset of the skin changes. A papillomatous condition of the cardiac end of the stomach is met with in rats fed on diets deficient in vitamin B_2. The histologic changes characteristic of inanition are present in rats dying as the result of a deficiency of vitamin B_2 Hypertrophy of the suprarenals occurs in rats lacking either vitamin B_1 or vitamin B_2. The histologic changes are similar to those produced by cold or slight degrees of toxemia.

AUTHOR'S SUMMARY.

TUMOURS OF MEDIASTINUM AND LUNG. T. SHENNAN, J. Path. & Bact. **31**:365, 1928.

This paper is based on thirty-one cases, all of which are described with considerable detail. Two of the tumors are sarcomas; twenty-five, carcinomas and four, thymomas. In at least thirteen of twenty-two primary carcinomas of the bronchus or lung, there was present old standing disease.

MIXED TUMORS OF THE FACE. P. MOULONGUET and A. PEYNET, Ann. d'anat. Path. **4**:957, 1927.

The face may give rise to mixed tumors which are identical to those found in the salivary gland. The tumors are usually small and have no particular clinical features. Their seat of predilection is in the region of the embryonic fissures, frontal, intermaxillary and lacrymonasal. It is possible that they originate from embryonic rests. The tumors are benign.

B. M. FRIED.

TUBERCULOSIS OF THE BREAST. PIETRO VERGA, Arch. per le sc. med. **49**:625, 1927.

Tuberculosis of the female mammary gland is rare and even more so is that of the male gland. The majority of cases in women appear between the twentieth and twenty-fifth years. Tuberculosis of the mammary glands occurs under three different aspects: (1) in the form of disseminated tubercles, (2) in the confluent form and (3) in the sclerosed form. Moreover, the disseminated form may pass over into the confluent form. All three of these forms can cause the formation of cavities and fistulas. Koch's bacillus, which is difficult to demonstrate, can enter the gland by way of the blood, by way of the lymphatics, through the lactiferous ducts and across a continuous solution of the skin of the nipple or of the areola.

A. J. SALLE.

FAMILIAL OSTEOPSATHYROSIS AND BLUE SCLEROTICS. E. APERT, BACH and ODINET, Bull. Soc. de pédiat. de Paris **26**:21, 1928.

The family in question consists of the father, mother and four children. The father and two of the children have fragile bones and blue sclerotics. The disease is regarded as a hereditary, faulty development of fibrous tissue as shown by thin sclerotics, thin eardrums and defective fibrous stroma with thinness and fragility of the long bones and deformed skull. The top of the skull may be depressed and there may be thickened areas above the ears.

MIGRATION OF ASCARIS AND OXYURIS INTO THE TISSUES OF INTESTINAL TUMORS IN MAN. S. ALFEEVA, Rev. de microbiol. et epidemiol. **6**:476, 1927.

A case of peritonitis is described resulting from perforation of an ascaris through a leiomyoma of the ileum. Microscopic examination revealed many passages of various standing — old ones pigmented and filled with scar tissue, and more recent ones with distended surrounding capillaries and slight cellular infiltration. One passage showing the features of an acute inflammatory process in its walls went through the tumor and communicated with the peritoneal cavity, and the adjacent evidences of acute inflammation here as contrasted with other parts of the peritoneum showed that this was where the ascaris had passed through.

In another passage oxyuris vermicularis was found, and in another, a calcified ascaris. Since ulceration from the side of the lumen did not occur, the perforation probably resulted from active movements of the helminth through the tumor. The leiomyoma was probably more easily penetrated than the normal bowel wall because of lack of contractility of the muscle fibers making it up and their disorderly arrangement.

ON THE SIMULTANEOUS OCCURRENCE OF BRONCHIECTASIS AND PULMONARY TUBERCULOSIS. H. KAUSCH and R. STEINERT, Beitr. z. Klin. d. Tuberk. **67**:498, 1927.

The clinical observations and the conditions found at autopsy in a patient, aged 19, are reported. Extensive bronchiectasis was found in the lower lobes, while the upper parts were occupied by an acute exudative tuberculosis with cavity formation. A similar case is reported without the observation made at autopsy.

MAX PINNER.

ALTERATIONS OF THE PULMONARY TISSUE AFTER THORACOPLASTY. M. STAEMMLER, Beitr. z. Klin. Tuberk. **67**:518, 1927.

Thoracoplasty was performed in a patient for empyema eighteen years before death. The anatomic-histologic observations in the collapsed lungs were as follows: In spite of the collapse of long standing, the anatomic picture shows little deviation from the normal. Some parts of the lung reexpanded slightly in handling. Even in such parts in which air is entirely absent, the alveolar epithelium is present, and the elastic fibers are unaltered. There is hardly any increase of connective tissue in the alveolar walls. The bronchial walls are not altered by atelectasis only. Where inflammatory processes are present, destruction of the elastic, muscular and cartilaginous elements occurs, and proliferation of connective tissue leads to pronounced alterations in the anatomic structure of the pulmonary tissue and of the bronchi.

MAX PINNER.

MORPHOLOGIC STUDIES ON CHRONIC VITAL STAINING WITH TRYPAN BLUE. HANS DIETERICH, Ztschr. f. d. ges. exper. Med. **57**:303, 1927.

Subcutaneous injections of trypan blue over a period of from five to ten months produced in three rats adenomatous-like new growths in the liver. In addition,

there were marked degenerative and proliferative changes in this organ. Degeneration of liver cells occurred early in the experiments; this was followed or accompanied by proliferation of the periportal stroma and hyperplasia of the liver cells. The author was unable to decide whether the hyperplasia of the liver cells was primarily due to stimulative action of trypan blue, or a regenerative process, the result of damage to the cells caused by the dye.

B. Lucké.

Hereditary Symmetrical Hypoplasia of Joints. D. G. Rochlin, Ztschr. f. Konstitutionslehre **13**:654, 1928.

Seven instances of symmetrical stiffening of the joints of both hands and feet in four generations of a family with a study of the condition in a father, aged 46, and his daughter are recorded. The anomaly is most commonly observed in the second, third, fourth and fifth interphalangeal joints of the hands and feet. The condition develops without changes in bone absorption and is a hereditary dominant according to Mendelian law.

F. R. Menne.

Morphologic Changes in Vitally Stained Animals. E. Komiya, Folia haemat. **35**:201, 1927.

Komiya investigated the peripheral blood in animals stained with different dyes. He found that after repeated injections of the stain, there occurs, at the beginning, an increase in the number of white cells which does not persist. In later stages, there is rather a tendency toward leukopenia. During the period of staining, there is an increase in the blood monocytes which show a characteristic distribution of the dye in their cytoplasm. Komiya's observations could not substantiate the opinion that all monocytes originate from the reticulo-endothelium. He also noted a tendency toward a rise in the mastzellen. Sheep's erythrocytes injected into the circulation of vitally stained rabbits are largely phagocytosed by the monocytes. A chronic vital staining calls forth the appearance of normoblasts in the blood.

B. M. Fried.

Acute and Chronic Leukemias. P. A. Barchasch, Folia haemat. **35**:229, 1927.

From a study of the literature and of six cases of acute and chronic leukemia, the author reached the conclusions that chronic and acute leukemia are but different expressions of the same disease. The cause of the disease is unknown, but it is closely related to that of sepsis. Moreover, the two varieties of leukemia run a clinical course akin to chronic and acute septicemia. The author thinks that in instances of an acute infectious condition, the possibility of a leukemia ought to be considered. Pathognomonic of acute leukemia is the onset with a necrotizing angina, high fever, splenic enlargement and hemorrhagic diathesis. The author could not confirm Nägeli's statement that in leukemic myelo-adenosis, the myeloblast infiltrates diffusely the liver while in leukemic lymphadenosis lymphomas are confined to the periportal areas. The differential diagnosis between acute and chronic leukemic lympho-adenosis and myelo-adenosis is based on the protease and oxydose reactions which are present in blood smears as well as in the bone marrow obtained by puncture of the sternum.

B. M. Fried.

Pernicious-Like Anemia in Children. O. Roth, Folia haemat. **35**:257, 1927.

Pernicious anemia is considered to be a disease affecting middle-aged persons only. Roth, however, quotes numerous French and German sources to the effect that a primary anemia having all the traits of the same disease as seen in the adult does occur in children. In the American literature, reports on this condi-

tion were made by Morse and Wolbach (*Am. J. Dis. Child.* **14**:301 [Oct.] 1917), and by Morse, who (Boston M. & S. J. **18**:657, 1922) published eighteen cases of infantile pernicious anemia observed by him. Roth studied a case of Biermer-Adisson's anemia in a girl weighing 13 Kg. (34 pounds) and measuring 90.5 cm. in length. (The author does not give her age, but judging from the photograph the child is 6 or 7 years old.)

The hemoglobin index in this case was high, there was a marked anisocytosis with the prominence of hemoglobin-rich megalocytes, a leukopenia with a pronounced lymphocytosis; there were also numerous normoblasts, numerous myeloblasts and a low platelet count. The gastric contents did not show any free hydrochloric acid. The temperature was elevated, the skin had a waxy yellowish tinge and was somewhat edematous. The Wassermann and the Pirquet tests were negative, the stools were negative for parasites or parasitic ova. The child improved under treatment with arsenic. Previous to her illness, she was fed largely on goat's milk. Roth is skeptical about the milk being the cause of the disease in his patient. He cites, however, a few instances in which infants fed with goat milk developed a hemolytic-like anemia. This is explained on the grounds that unsaturated fatty acids in which goat milk is rich reached through the intestinal tract the blood stream, thus causing hemolysis.

B. M. Fried.

The Blood Count of Macacus Rhesus. Herbert Fox, Folia haemat. **35**:272, 1927.

The studies on blood count made by Fox confirmed in general the previous investigations published by Sabin and by Shaw. They showed that in M. rhesus there is a cycle during the working day and also a high count during the night. Fox did not notice that a rhythm takes place during the daytime. The documents are to the effect that the neutrophils are largely responsible for the variations during twenty-four hours.

B. M. Fried.

The German Literature on Anemia for 1926: A General Review. T. Zadek, Folia haemat. **35**:281, 1927.

A comprehensive review on different forms of anemia was published in the German language in 1926. The bibliography includes seventy-seven full references.

B. M. Fried.

Hemorrhagic Diatheses: A Review for 1926. Werner Schultz, Folia Haemat. **35**:303, 1927.

This is a brief review on hemorrhagic diatheses including almost exclusively German names.

B. M. Fried.

Primary Carcinoma of the Male Urethra. A. Fukai, Acta Derm. **11**:1, 1928.

There are now recorded (including four cases reported by Fukai) something like eighty-four cases of urethral carcinoma. This form of carcinoma has occurred mostly between the ages of from 45 to 65 years. It is noteworthy that urethral carcinoma frequently develops on a basis of a gonorrheal or traumatic stricture. The part involved most frequently is the pars cavernosa. It concerns practically always a flat cell carcinoma.

Cutaneous Horn of Rare Magnitude. Y. Hotta, Acta Derm. **11**:243, 1928.

The horn, which was on the right side of the face of a woman, aged 81, was 4.8 cm. in length.

Pathologic Chemistry

THE PURIFICATION OF HEPARIN AND ITS CHEMICAL AND PHYSIOLOGICAL REACTIONS. W. H. HOWELL, Bull. Johns Hopkins Hosp. **42**:199, 1928.

A method is described for the purification of crude heparin which gives a product free from phosphorus and nitrogen. Its anticoagulant action for human blood is of the order of from 1 mg. to 100 cc. of blood. The reaction of the purified heparin shows that it is a carbohydrate body, apparently a glycuronic acid compound. The use of the purified heparin as a safe anticoagulant for blood transfusions is suggested. Glycuronic acid prepared from euxanthic acid does not have an anticoagulant action, but when heated to 250 C., it yields a compound with distinct anticoagulant properties.

AUTHOR'S SUMMARY.

THE SURFACE TENSION OF HUMAN BLOOD UNDER NORMAL AND PATHOLOGICAL CONDITIONS. ELIZABETH G. NICHOLLS, Bull. Johns Hopkins Hosp. **42**:358, 1928.

The surface tension of normal human blood serum, as measured by the tensiometric method of du Noüy, is remarkably constant with regard to both the initial value and the time-drop. Only a slight decrease in the initial surface tension and time-drop is caused by the ingestion of lipoid-rich food. Variations of the surface tension of the blood serum have been found to occur as follows: Low surface tension with a variable time-drop ranging from less to considerably greater than normal appears to accompany hyperbilirubinemia due to jaundice; the more severe the jaundice as measured by the van den Bergh reaction, the greater the time-drop. Association of hyperbilirubinemia with hypocholesterolemia is found with low surface tension in pernicious anemia. Low surface tension in malignancy seems usually to be associated with an increase in serum bilirubin. Low surface tension values and a persistent decrease in the time-drop are found in conditions in which there is a hypercholesterolemia and lipemia, as in nephrosis and some cases of diffuse nephritis. In uremia, low surface tension and a decreased time-drop is found in association with normal serum bilirubin and normal or slightly increased blood cholesterol. In hyperthyroidism, low surface tension is associated with a normal bilirubin value and a hypocholesterolemia. In leukemia, low surface tension and a decreased time-drop is observed with hypobilirubinemia and hypocholesterolemia.

AUTHOR'S SUMMARY.

PANCREATIC FAT NECROSIS: A CHEMICAL STUDY. FREDA K. HERBERT, Brit. J. Exper. Path. **9**:57, 1928.

The omental fat from cases of human acute pancreatitis and experimental fat necrosis in rats and cats was investigated histologically and chemically. The histochemical observations confirmed the accepted opinion that soap is formed in the necrotic areas. Chemical analysis revealed the occurrence of hydrolysis and saponification, but the hydrolysis was mainly an acid one and little soap was formed. A marked rise in the calcium content of the omental tissue in extensive necrosis was noted, but only a minute proportion existed as soap.

S. D. SIMON.

BLOOD PHOSPHORUS IN HEALTH AND DISEASE. F. B. BYROM and H. D. KAY, Brit. J. Exper. Path. **9**:72, 1928.

In an adequately large series of cases, the blood phosphorus did not differ significantly in nonanemic, noncancerous controls and nonanemic cancerous subjects. When changes in various phosphorus compounds were found in cases of malignant disease they were always explicable on the basis of an accompanying anemia, and did not differ in this respect from noncancerous anemias. The Gróbly "phosphorus quotient" was not of value in the diagnosis of malignant disease.

The changes in phosphorus distribution in simple secondary anemia differed sharply from those of pernicious anemia and the anemia accompanying chronic nephritis. The blood phosphorus in the leukemia varied not only with the anemia but with the number of leukocytes, since these cells contain several times the amount of phosphorus that an equal volume of red blood corpuscles contains.

S. D. Simon.

The Chemistry of Gaucher's Substance. H. Beumer, Klin. Wchnschr. **7**: 758, 1928.

Beumer analyzed a spleen removed from a child, aged 4 years, because of Gaucher's Disease. The spleen weighed 170 Gm. Qualitative tests demonstrated the presence of both kerasin and cerebron.

E. F. Hirsch.

Copper in Human Blood Serum. H. A. Krebs, Klin. Wchnschr. **7**:584, 1928

The cystein method used by Krebs in determining the copper content of the blood serum is based on the catalytic oxidizing properties of copper. The fluid to be examined is shaken with clear cystein and sodium pyrophosphate. The amount of oxygen used in the reaction measured by the manometer method allows the calculation of the copper content.

It was found that the average copper content of the serum was more than twice as high in pregnant women as in normal persons. The content was also increased in pulmonary tuberculosis, diphtheria, endocarditis, scarlet fever and leukemia, but was found lower than normal in three cases of disorder of the kidneys.

Physicochemical Studies on the Serum of Patients with Scarlet Fever. Endre Tüdös and Alfred Ebel, Ztschr. f. d. ges. exper. Med. **57**:709, 1927.

The electrolyte content (determined by conductivity measurements), and the sodium chloride content (determined by titration) of the serum of patients with scarlet fever is somewhat decreased. Renal complications during scarlet fever do not materially alter these observations.

B. Lucke.

Microbiology and Parasitology

Pericarditis as a Primary Clinical Manifestation of Tuberculosis in Childhood. Maurice L. Blatt and Joseph Greengard, Am. J. Dis. Child. **35**:631, 1928.

Pericarditis as the first clinical manifestation of active tuberculosis in childhood is rare, but may occur. A case, with autopsy, is reported, and the pathology, symptomatology, diagnosis and therapy are discussed. Prognostically, this type of case is thought to belong to the malignant class of tuberculous infections similar, in this regard, to meningeal involvement.

Pearl Zeek.

Rheumatic Nodules: Their Incidence in Rheumatic Infections. Katherine Merritt, Am. J. Dis. Child. **35**:823, 1928.

Two hundred and twenty-four patients showing rheumatic infections were observed during the autumn, winter and spring of the years 1924 to 1927. Twenty-five children showed nodules, three of them in more than one attack. They appeared most frequently in patients with severe cardiac involvement and pointed to a poor prognosis. The nature of rheumatic nodules is discussed, and the opinions of various authors on the subject are reviewed.

Pearl Zeek.

THE MASS DIAGNOSIS OF HOOKWORM INFECTION. CLAYTON LANE, Am. J. Hyg. **8**: supplement, 1, 1928.

Exception is taken to the statement made several years ago that microscopic examination of feces for the detection of hookworm ova is of little diagnostic value. A method of mass diagnosis is described which meets the requirements of scientific accuracy, simplicity and economy of time and materials. In brief, the method is as follows: 1 cc. of feces is collected, diluted and shaken vigorously and then centrifugalized; the supernatant fluid is poured off; it is diluted again with three-fourths saturated salt solution; centrifugalized at 1,000 revolutions per minute for one minute with the cover slip in contact with the free surface of the liquid; the cover slip is removed sharply, and the material prepared as hanging drop, herded and examined. The technic is described in great detail and the method termed "direct centrifugal floatation" (D. C. F.). Comparison with various other methods and with adequate controls demonstrates the superior accuracy of D. C. F. Its application on a mass scale is advocated, feces being collected by unskilled field workers and the examinations being made by a single skilled chief. Wholesale treatment of an entire population without individual diagnosis is deplored on political, moral and economic grounds, and D. C. F. is proposed as affording an adequate and humane method of estimating and controlling hookworm infestation in such a population.

AMOEBIASIS IN KITTENS INFECTED WITH AMOEBAE FROM ACUTE AND "CARRIER" HUMAN CASES AND WITH THE TETRANUCLEATE AMOEBAE OF THE MONKEY AND PIG. J. F. KESSEL, Am. J. Hyg. **8**:311, 1928.

Kittens were infected by mouth and by rectum with dysentery amebas from human "carriers" who did not give a history of having had dysentery. They developed the same dysenteric symptoms and exhibited the same lesions as kittens similarly infected with amebas from human cases of amebic dysentery, thus emphasizing the importance of host resistance rather than parasite virulence. Evidence was not found to support the view (of Brumpt) that two morphologically identical species of amebas exist, of which one is pathogenic and the other nonpathogenic. Amebas obtained from naturally infected kittens, from monkeys and from domestic pigs produced symptoms and pathologic changes similar to those caused by the dysentery ameba of man, and the conclusion is drawn that they are in all probability one and the same species.

S. D. SIMON.

SPONTANEOUS STREPTOCOCCUS INFECTIONS IN GUINEA PIGS. ELIZABETH I. PARSONS and ROSCOE R. HYDE, Am. J. Hyg. **8**:356, 1928.

A resumé of the history of spontaneous streptococcus infections in guinea-pigs is given together with the data concerning an epizootic among a colony of complement deficient guinea-pigs. Both the chronic lymphadenitis and the acute pneumonic and puerperal types were present. A complete bacteriologic examination of the seventy-seven strains of hemolytic and nonhemolytic streptococci isolated is here recorded. The results of a few experimental infections produced by the streptococci isolated are given.

AUTHORS' SUMMARY.

COUNCILMANIA TENUIS AND C. DISSIMILIS, INTESTINAL AMEBAS OF MAN. I. C. A. KOFOID, Arch. Int. Med. **41**:558, 1928.

CULTURE METHODS, ENCYSTMENT AND EXCYSTMENT OF COUNCILMANIA DISSIMILIS KOFOID, IN CULTURE. II. E. A. ALLEN, ibid. 574.

PRESENTATION OF CASE OF INFECTION WITH COUNCILMANIA DISSIMILIS KOFOID. III. L. M. BOYERS, ibid. 579.

I. In this discussion and morphologic comparison of many intestinal amebas of man, it is suggested that the name *C. tenuis* be given the ameba previously

presented as *Entamseba tenuis*, and *C dissimilis* to a species of ameba heretofore included as a form of *Endamoeba dysenteriae*. Differentiation of species of human intestinal amebas may be made by study of nuclear structure in matured cysts found in fecal smears stained by iron hematoxylin. Nuclear structure may also be used as one basis of distinguishing the genus of ameba.

II. Cultural studies of *C. dissimilis* and *E. dysenteriae* have demonstrated many points of difference. In Locke's egg-albumin medium, *C. dissimilis* grows indefinitely, while *E. dysenteriae* dies out after a few transfers. *C. dissimilis* showed both encystment and excystment in culture, while by the same methods no such results were obtained with *E. dysenteriae*. There were also morphologic differences between the two forms in culture.

III. A case is presented with infection by *C. dissimilis*, and mixed infection by other intestinal protozoons, including a consideration of certain therapeutic procedures against such parasites.

H. R. FISHBACK.

BACTERIOLOGIC EXAMINATION OF SPUTUM FROM 724 PATIENTS WITH BRONCHIAL ASTHMA. I. C. WALKER and J. ADKINSON, Arch. Int. Med. **41**:601, 1928.

Cultures were made of the bronchial sputum of patients with the nonsensitive type of asthma. Bacteria were isolated from plate cultures, and identified in subculture. Streptococci were divided into subgroups according to Holman's classification. The study has been carried on for the last nine years.

Streptococci were the most important organisms so far as frequency of occurrence and numbers are concerned. In more than one third of the specimens of sputum, only one variety of streptococcus was recovered, and it was unusual to find more than three varieties in one specimen. Usually also a small number of varieties were predominant in a single season, although these varieties might change from year to year. *Staphylococcus pyogenes aureus* was the only other bacterium recovered in sufficient numbers to be comparable to the streptococci.

H. R. FISHBACK.

THE MECHANISM OF TOXIN PRODUCTION BY CLOSTRIDIUM BOTULINUM. GAIL M. DACK and WILLARD L. WOOD, J. Infect. Dis. **42**:213, 1928.

Supernatant fluid from a forty-eight-hour beef heart culture of *Clostridium botulinum*, type A, when added to thymolized beef heart, egg white and casein mediums, on incubation, showed the following changes: the toxin was much weakened but not completely destroyed, and there was evidence of proteolytic activity. Similar results were obtained when the cell suspensions were added to thymolized beef heart medium.

The toxin was completely destroyed in the thymolized cell suspensions and supernatant fluid, in the absence of added protein mediums.

AUTHORS' SUMMARY.

A CASE OF B. ENTERITIDIS SEPTICEMIA. CHEN-PIEN LI and YIN-YUAN NI, J. Infect. Dis. **42**:226, 1928.

A case of septicemia caused by *Bacillus enteritidis* (Gärtner), with a febrile course for about three weeks, with purpuric rash over the entire surface of the body, is reported. The diagnosis was made by serologic tests as well as by the isolation of *B. enteritidis* from the blood, urine, feces and saliva.

AUTHORS' SUMMARY.

AN APPARENTLY UNDESCRIBED HEMOLYTIC ANAEROBIC DIPLOCOCCUS. SARA E. BRANHAM, J. Infect. Dis. **42**:230, 1928.

Two strains of a tiny, gram-negative, hemolytic diplococcus have been isolated from nasopharyngeal washings of persons with old colds. These cocci are uniformly

round, and occur chiefly in pairs. They are fastidious in their requirements for growth in regard to p_H, temperature and composition of culture mediums; and they require a marked degree of anaerobiosis. They produce hydrogen sulphide and indol, and some acid in dextrose broth and in milk. They occasionally produce traces of gas in beef heart medium, and one strain slowly liquefies gelatin. They have not been pathogenic for rabbits, guinea-pigs and mice, nor were they filtrable through Berkefeld V filters under the conditions of the experiments. They are closely related to each other serologically, but quite distinct from the micro-organisms of Holman and Krock and of Hall and Howitt. Cultural differentiation in this group is less definite.

Although these two strains are apparently quite distinct from *Staphylococcus parvulus* or *Micrococcus gazogenes*, it does not seem advisable to name them as a new species until more than two strains have been found.

AUTHOR'S SUMMARY.

A NEW DIFFERENTIAL MEDIUM FOR THE PARATYPHOID GROUP. EDWIN O. JORDAN and PAUL H. HARMON, J. Infect. Dis. **42**:238, 1928.

The differential medium of Brown, Duncan and Henry has not proved as successful in differentiating the Schottmüller and Aertrycke types as a new medium described in this paper. This new medium is composed of simple, inexpensive ingredients and has given a perfectly definite differentiation with a large number of strains (eighty-seven *Bacillus aertrycke* and forty-five *Bacillus schottmülleri)* previously identified by the agglutinin absorption method.

AUTHORS' SUMMARY.

THE INACTIVATION OF THE CHICKEN-TUMOR VIRUS BY MEANS OF CALCIUM COMPOUNDS. MARGARET REED LEWIS and HOWARD B. ANDERVONT, Bull. Johns Hopkins Hosp. **42**:191, 1928.

The addition of calcium oxide, calcium monobasic phosphate and calcium hexose phosphate in as small amounts as 0.5, 0.75 and 1 per cent, respectively, to the chicken-tumor extract (1 : 10) inactivated the virus and prevented the growth of a tumor. The addition of large amounts (25 per cent) of calcium carbonate to the tumor extract adsorbed and fixed the virus. Small amounts (1 per cent) sometimes inactivated the virus but more frequently, although the virus was partly adsorbed, it was not fixed by this amount of calcium carbonate. The addition of 2 per cent of plaster of Paris to the tumor extract inactivated the virus, but when only 1 per cent of plaster of Paris was added to the extract, both the supernatant fluid and the washed deposit caused the growth of a tumor when injected into the breast of a chicken.

AUTHORS' SUMMARY.

STUDIES IN EXPERIMENTAL SYPHILIS. ALAN M. CHESNEY, THOMAS B. TURNER and CHARLES R. L. HALLEY, Bull. Johns Hopkins Hosp. **42**:319, 1928.

A series of experiments has been performed in which rabbits with either healed or granulating wounds (or both) on their backs were subsequently inoculated intratesticularly or intravenously with a virulent strain of *Spirochaeta pallida*. In each instance, syphilitic lesions developed in the scars of the wounds. These lesions exhibited a marked tendency to conform to the pattern of the scars. The incubation period of the lesions developing after intravenous inoculation corresponded closely with that of lesions which developed at the site of inoculation after subcutaneous injection. From this it is inferred that shortly or immediately following intravenous inoculation, the spirochetes reach the scar and are deposited there. The histories of two patients are presented, in whom syphilitic lesions developed in previously traumatized areas of the skin, when the syphilitic infection was acquired subsequent to the injury. It is concluded that recent nonspecific inflammatory reactions of the skin of both rabbits and human beings, resulting from

wounds, constitute foci favorable for the lodgement and growth of *Spirochaeta pallida* coming from within the body, and predispose to the evolution of syphilitic lesions in those areas.

AUTHORS' SUMMARY.

ENCEPHALITIS AS A COMPLICATION OF MEASLES. J. H. MUSSER and G. H. HAUSER, J. A. M. A. **90**:1267, 1928.

In eight cases of encephalitis occurring in the course of measles, the striking feature of the condition when observed grossly was the presence of numerous discrete punctate hemorrhages throughout the brain. Microscopically, the observation peculiar to this type of encephalitis was perivascular hemorrhage about some of the small vessels of the brain. None of these cases presented any clinical or postmortem evidence of tuberculosis or of syphilis.

AUTHORS' SUMMARY.

PNEUMOCOCCAL TYPES IN ACUTE MASTOIDITIS AND MENINGITIS. JOHN T. BAUER and HUSTON ST. CLAIR, J. A. M. A. **90**:1429, 1928.

In eighteen cases of "primary" pneumococcus infection of the mastoid cells and meninges in which the organisms have been typed, type III pneumococci predominate in the cases following otitis media, and type IV pneumococci in meningitis without a history of otitis media.

AUTHORS' SUMMARY.

DETERMINATION OF VIRULENCE OF DIPHTHERIA BACILLI BY ELECTROPHORESIS. L. B. JENSEN and I. S. FALK, J. Bact. **15**:367, 1928. L. B. JENSEN, I. S. FALK, F. O. TONNEY and J. L. WHITE, ibid., p. 413. I. S. FALK, L. B. JENSEN and J. H. MILLS, ibid., p. 421.

In this series of three papers by Falk, Jensen and their co-workers, an attempt has been made to apply the established relationship between electrophoretic mobility of bacteria and their virulence to the problem of virulence of the diphtheria bacillus. It was pointed out that if one took an arbitrary division point for virulence (toxicogenicity), or nonvirulence, the strains of high virulence as measured by the guinea-pig method showed low electrophoretic mobility, while those of low virulence showed a high degree of mobility. There was some parallelism, moreover, between the degree of toxicogenicity and the potential difference. Checking by means of the guinea-pig test gave results almost uniformly parallel, and when this was not the case the electrophoretic method erred on the side of safety, i. e., strains were considered virulent by electrophoresis although they would not be so considered by the guinea-pig method.

Finally, by simplifying the apparatus and technic, the authors propose electrophoretic measurements of virulence as a substitute for the older guinea-pig method with its disadvantages of expense and time.

EDWIN P. JORDAN.

THE PRODUCTION OF SKIN NECROSIS BY CERTAIN AUTOLYSATES OF PNEUMOCOCCUS (TYPES I AND II). JULIA T. PARKER, J. Exper. Med. **47**:531, 1928.

Certain pneumococcus autolysates produce necrosis when injected into the skin of guinea-pigs. The necrosis producing principle can be filtered through a Berkefeld N filter, is extremely thermolabile, and is sensitive to oxidation. The necrotizing poison can be separated from the pneumococcus hemotoxin by adsorption with red cells. This removes the hemotoxin and leaves the necrosis producing principle unaffected. The necrotizing substances obtained from pneumococcus types I and II are neutralized by the antiserum prepared with pneumococcus I.

AUTHOR'S SUMMARY.

THE INTERCONVERTIBILITY OF "R" AND "S" FORMS OF PNEUMOCOCCUS. MARTIN H. DAWSON, J. Exper. Med. **47**:577, 1928.

Single cell cultures of "R" pneumococci may revert in all respects to the "S" type. In all instances in which reversion has occurred, the "R" forms have

invariably reverted to the same specific type from which they were originally derived. The transformation "R" to "S" may be effected in viro by growth in anti- "R" serums, as well as in vivo by the method of animal passage. Reversion from "R" to "S," whether effected in vivo or in vitro, is always accompanied by the acquisition of maximal virulence.

AUTHOR'S SUMMARY.

THE INFLUENCE OF VACCINIA ON THE REACTION TO INFECTION IN RABBITS WITH SYPHILIS. LOUISE PEARCE, J. Exper. Med. **47**:611, 1928.

Experiments are reported in which the effect of a concomitant infection, vaccinia, on the syphilitic reaction of rabbits was studied. Vaccine virus was inoculated intracutaneously on the side of the body at the time of intratesticular inoculation with *Spirochaeta pallida*. The results showed clearly that the vaccination caused a profound disturbance in the syphilitic reaction, the ensuing syphilis being extremely severe. From an analysis of various features of the reaction, it appeared that the factor of host resistance was primarily concerned in the effects observed.

AUTHOR'S SUMMARY.

THE MODE OF SPREAD OF A FRIEDLÄNDER BACILLUS-LIKE RESPIRATORY INFECTION OF MICE. LESLIE T. WEBSTER, J. Exper. Med. **47**:685 (May) 1928.

This Friedländer bacilli infection in mice takes several clinical courses, depending on variations in host reaction and not depending on bacterial variation. The particular type of infection manifested is determined by the degree of resisting power displayed by the infected animals at the moment that the infection occurred and progressed.

INFLUENCE OF MALARIA AND SPLENECTOMY ON OROYA FEVER IN MONKEYS. H. NOGUCHI, J. Exper. Med. **47**:821, 1928.

Malaria and splenectomy, singly or combined, did not have an appreciable effect on the course of oroya fever in the monkey.

EXPERIMENTS ON THE VISIBILITY OF THE POLYHEDRAL VIRUSES. R. W. GLASSER and E. V. COWDRY, J. Exper. Med. **47**:829, 1928.

With the technics employed, we have not been able to detect any qualitative differences between the particles visible in normal blood and in blood from persons with wilt disease and grasserie. Of the two conditions we can speak more definitely in the case of grasserie, because we have studied this quantitatively as well, that is to say, the particles visible microscopically and ultramicroscopically have been counted without bringing to light any marked difference between normal and diseased blood. Thus leads us to believe that the virus of wilt disease is probably invisible, and the virus of grasserie almost certainly so, when studied with the optical equipment that we have used, and that further evidence will be necessary before one can accept *Chlamydozoa* or *Borrellina* as the active etiologic agents. Although these two polyhedral viruses do not appear to be visibly particulate, it does not follow that other filtrable viruses are not organized in this way. Each should be considered on its own merits.

AUTHORS' SUMMARY.

EFFECT OF FORMALIN ON THE VIRUS OF VESICULAR STOMATITIS OF HORSES. PETER K. OLITSKY and PERRIN H. LONG, J. Exper. Med. **47**:835, 1928.

The virus of vesicular stomatitis is not readily killed by formaldehyde. This chemical is one of a group which coagulates the proteins of the medium in which the virus is usually contained. It has already been found that other reagents of the protein-coagulating group are not actively virucidal, and the effect of formaldehyde in this instance is therefore characteristic of the group. The

so-called formalinized vaccines which give rise to immunity can be shown to have done so because of the presence of living virus. A single injection of such so-called "vaccine," or of other material containing living virus, is capable of inducing immunity in guinea-pigs. Protection, however, does not follow a single injection of dead virus. Furthermore, repeated inoculations of virus killed by formaldehyde likewise fail to induce resistance against subsequent injections of the living virus. It is concluded, with respect to the virus of vesicular stomatitis, that the use of formalin has failed to solve the problem of active immunization with dead virus.

AUTHORS' SUMMARY.

BACTERIAL VARIATION IN CULTURES OF FRIEDLÄNDER'S BACILLUS. LOUIS A. JULIANELLE, J. Exper. Med. **47**:889, 1928.

Under proper conditions, mass R cultures of Friedländer's bacillus may give rise to a number of variants which are dissimilar in colony appearance and in form and structure. Three such forms have been described. In two varieties, differences have been observed not only in colony formation and form and structure, but in cultural and antigenic characters. None of the methods employed were adequate to cause reversion of any of the R variants to the S type. Growth of the R2 variant in its own antiserum, however, induced a change to the R1 form. R forms of Friendländer's bacillus may be derived from S strains by aging or by growth in anti-S serum of the homologous type. R strains may be isolated in culture directly from infection. In the cases in which R forms were found, S cells were also present, and the pathologic condition was of a chronic nature.

AUTHOR'S SUMMARY.

UDDER INFECTION WITH STREPTOCOCCI OF THE SCARLET FEVER TYPE. F. S. JONES and RALPH B. LITTLE, J. Exper. Med. **47**:945, 957 and 965, 1928.

Spontaneous and Experimental Infection of Udders.—The clinical and bacteriologic manifestations in two cows the udders of which became infected under natural conditions with hemolytic streptococci of the scarlet fever type are discussed. One of the cows was found in a herd supplying raw milk to a small town in which a milk-borne outbreak of scarlet fever had occurred a short time before. When small numbers of the streptococcus obtained from this cow were injected into the udder of a normal cow, severe mastitis accompanied by a well marked general reaction resulted. Evidence leads to the conclusion that a severe attack of mastitis due to this organism in one quarter does not sufficiently immunize the other quarters to protect them completely, since the streptococcus can be readily implanted in them. The secondary infections were much milder than the original process.

A Study of the Scarlet Fever Type of Streptococci Isolated from the Udder of the Cow.—The streptococcus isolated from the udder of a cow on a farm where an outbreak of scarlet fever originated has been correlated with known scarlet fever strains. This streptococcus and another also isolated from the udder of a cow are indistinguishable in cultural characters and certain antigen affinities from *S. scarlatinae*. Skin tests indicate that the strain isolated from the milk of the cow in a herd to which the epidemic of scarlet fever was attributed produced a toxin which was neutralized with scarlet fever antitoxin.

The Influence of Milk on the Growth of Scarlet Fever Streptococci.—The experiments indicate that milk filtered through a Berkefeld candle V or heated at 58 C. for twenty minutes when added to blood agar plate cultures interferes with the development of colonies of the scarlet fever streptococcus. The inhibition observed is proportional to the amount of milk. When the approximate dilution of milk in the Petri dish is 1:20 or 1:25, growth of the organisms is completely suppressed or only a small proportion of nonhemolytic colonies develop. As the amount of milk is decreased the colonies become larger and their hemolytic zones more pronounced, although even when the final dilution of milk reaches

1:100 or 1:125 only colonies easily mistaken for the narrow zoned bovine streptococci appear. The effects on the surviving organisms would appear to be transient, since both the nonhemolytic colonies and those with small zones manifest the original hemolytic properties when transferred to other media. When scarlet fever streptococci are added in small quantities to milk heated at 58 C. for twenty minutes and incubated, growth is inhibited. If the period is prolonged, the streptococci are killed. When such mixtures are refrigerated, some of the streptococci are killed but others survive the test period.

AUTHORS' SUMMARIES.

CUTANEOUS SPIROCHAETOSIS DUE TO TREPONEMA CUNICULI IN BRITISH RABBITS. D. K. ADAMS, D. F. CAPPELL and J. A. W. MCCLUSKIE, J. Path. & Bact. **31**:157, 1928.

The authors describe lesions of the skin which appear in the anogenital regions and on the nose of both wild and domestic rabbits in the British Isles. The infection is believed to be conveyed by coitus, and a spirochete, *Treponema cuniculi*, indistinguishable from *Treponema pallidum* has been isolated from the lesions and seems to be the etiologic factor. The lesions produced by *Treponema cuniculi* are confined to the superficial layers of the skin, where large numbers of organisms may be found.

It is pointed out that the infection may constitute an important source of error in work on human syphilis in the rabbit.

E. M. HALL.

PRACTICAL APPLICATION OF THE DIRECT OXIDASE REACTION IN BACTERIOLOGY. J. GORDON and J. W. MCLEOD, J. Path. & Bact. **31**:185, 1928.

The authors make use of the oxidase reaction of certain bacteria which grow well only in the presence of oxygen in differentiating their colonies on plates. These bacteria contain a thermolabile direct oxidase system which can be revealed by bringing their colonies into contact with a 1 per cent solution of dimethyl-paraphenylene-diamine hydrochloride and subsequently exposing them to air. The dye is absorbed by the colonies and rapidly oxidized through a red tint to black. Members of closely related groups apparently react in a similar manner. Thus gonococci, meningococci and the gram-negative cocci of the pharynx can be differentiated from *Staphylococcus albus* by this reaction, the first acting positively and the last negatively. *B. coli* and *V. cholerae* can also be differentiated by this method. *V. cholerae* gives the oxidase reaction, while *B. coli* does not. The authors give a list of the bacteria that have been tested for oxidase with their reactions.

E. M. HALL.

THE PURPURA PRODUCING SUBSTANCE IN PNEUMOCOCCUS AND THE HERITABLE SUSCEPTIBILITY OF MICE. W. MAIR, J. Path. & Bact. **31**:215, 1928.

Pneumococci contain a substance which causes purpuric hemorrhages in white mice, especially in animals selected by inbreeding.

AUTHOR'S SUMMARY.

EXPERIMENTAL MONOCYTOSIS: EFFECTS OF DEAD BACTERIUM MONOCYTOGENSES AND OF EXTRACTS OF LYMPHATIC GLANDS. L. J. WITTS, J. Path. & Bact. **31**:249, 1928.

The monocytes of the rabbit are increased by single injections of killed *B. monocytogenes* or emulsions of lymphatic tissue. The increase is not commensurate with that occurring in infection caused by *B. monocytogenes*.

AUTHOR'S SUMMARY.

FURTHER INVESTIGATIONS ON SELECTIVE BACTERICIDAL ACTION. E. ASHLEY COOPER and JOHN MASON, J. Path. & Bact. **31**:343, 1928.

The biologic differentiation of germicides into "physicochemical" and "chemical" types has been further studied with the following results: Dyes such as brilliant

green, malachite green and crystal violet have been found to behave as "chemical" germicides, attacking *B. coli* preferentially to the *B. pyocyaneus (Pseudomonas aeruginosa), B. fluorescens nonliquefaciens (Pseudomonas nonliquefaciens)* and *B. fluorescens liquefaciens (Pseudomonas fluorescens)* group. This is in agreement with modern views as to their chemical action on proteins. *B. mesentericus* behaves somewhat similarly to *B. fluorescens nonliquefaciens,* etc., in being sensitive to certain "physicochemical" germicides, e. g., phenols. *B. proteus,* although more susceptible than *B. coli* to disinfection by heat, exhibits a greater resistance to phenol and alcohol. The thermophilic organisms are highly resistant to the action of the "physicochemical" disinfectants. This resistance is, however, extended to certain of the "chemical" disinfectants (e. g., hydrogen peroxide, benzoquinone), although the thermophils are extraordinarily susceptible to the action of certain dyes. Substances exerting a chemical reducing action are more highly germicidal toward *B. coli* growing aerobically than under anaerobic conditions. Evidence is brought forward to show that this explains why reducing agents are classified by the bactericidal tests as "physicochemical" germicides in consequence of their selective action on the aerobic *B. fluorescens nonliquefaciens.* The influence of time and temperature on selective action has been investigated. Under all experimental conditions examined, phenol attacks the *B. pyocyaneus* group preferentially, thus behaving as a "physicochemical" germicide. This type of selective action is thus not determined by environmental factors but is probably associated with the internal colloidal condition of the organisms. Certain other disinfectants (e. g., picric acid and quinone) behave alternately as "physicochemical" and "chemical" germicides according to experimental conditions. Explanations of this anomaly are advanced. Evidence has not been obtained that phenol catalyzes the action of hot water. This conclusion correlated with the foregoing results obtained with *B. proteus* and thermophilic organisms points to the existence of differences in the mechanism of the germicidal action of heat and of the "physicochemical" germicides.

AUTHORS' SUMMARY.

PREVENTION OF SYPHILIS. C. LEVADITI, in collaboration with V. SANCHIS-BAYARRI, R. SCHOEN and Y. MANIN, Ann. de l'inst. Pasteur **42**:105, 1928.

Tellurium and bismuth compounds, used as preventives, confer a lasting antisyphilitic state. This state is shown as much by the nonopening of a chancre following the inoculations, practiced at different times and at different intervals, as by the sterility of the popliteal ganglions. The animal remains then without apparent infection, which puts the bismuth and tellurium compounds in the same class with the best known antisyphilitics. Bismuth compounds are even superior, in the sense that the duration of prevention exceeds the protection conferred by arsphenamine or by the arsenic derivatives administered by mouth.

The preventive action is a function of the dose of metal injected and of the nature of the product used. The renal metallic potential reflects faithfully the degree of prevention. In fact, it does not suffice that the metal should be present in the tissues for efficacious protection; still, it is necessary that the metallic rate of the organs and particularly of the kidney attain values below which a prophylactic action, or even a curative action, would not be manifested. It is the same with the chemical constitution or with the physical state of the element administered. With equal doses of bismuth or tellurium compounds, certain products are more active than others (as, for example, the insoluble derivatives of bismuth, in comparison with the finely divided element itself). In the last analysis, all depends on the more or less rapid and perfect elaboration of complex metal-protein compounds, which assure the lysis of spirochetes, and consequently prevent or cure the treponema infection.

AUTHOR'S CONCLUSIONS.

RÔLE OF THE CENTRAL NERVOUS SYSTEM IN MORBID LOCAL PROCESSES. SPERANSKY, Ann. de l'inst. Pasteur **42**:179, 1928.

A previous article, appearing in the September, 1927, number of the French journal (abstr., ARCH. PATH. **5**:534 [March] 1928) is expanded. "If we admit

that toxic processes were of exclusively nervous origin, we ought equally to attribute to the nervous system a kind of protective rôle in septic processes, that is, in the processes which produce primary lesions in local tissues."

M. S. MARSHALL.

INFECTIOUS NECROTIC HEPATITIS (BRAXY, BLACK DISEASE) OF AUSTRALIAN SHEEP. A. W. TURNER, Ann. de l'inst. Pasteur **42**:211, 1928.

The pathogenic agent of this disease is a strain of *B. oedematiens* (Weinberg and Séguin). One may reproduce in guinea-pigs and in sheep the clinical picture and the anatomic lesions observed in the spontaneous disease. It is possible to immunize guinea-pigs or sheep with one or several injections of formalinized anaculture. Ten vaccinated sheep have all resisted test injections (four controls died, and one became gravely ill). An experiment made on a large scale and under natural conditions would be necessary to evaluate exactly the practical value of immunization.

AUTHOR'S CONCLUSIONS.

EXPERIMENTAL STUDIES IN REINFECTION IN HEALED TUBERCULOSIS. H. DOLD, Beitr. z. klin. d. Tuberk. **67**:524, 1927.

Forty guinea-pigs were infected intracutaneously with a tubercle bacillus of low virulence which caused only localized lesions. Thirty days later, the tuberculous focus was removed surgically. Three and one-half months after the first infection, the same guinea-pigs were infected with virulent bacilli. They behaved exactly the same as untreated animals. In another series of animals, the first focus of infection was not removed, but healed spontaneously. Reinfection after six months showed that these animals had not acquired immunity. A healed slight infection does not confer immunity to guinea-pigs.

MAX PINNER.

MORPHOLOGY OF THE BLOOD DURING PNEUMOTHORAX TREATMENT IN PULMONARY TUBERCULOSIS. R. RUSSEW, Beitr. z. klin. d. Tuberk. **68**:522, 1928.

Serial differential counts are helpful in the prognosis and treatment with pneumothorax. The disappearance of a polynucleosis and of shifting to the left, replaced by a gradual lymphocytosis and an increase in the eosinophils, indicates good prognosis.

MAX PINNER.

MATÉFY'S REACTION IN PULMONARY TUBERCULOSIS. S. ERLANDSSON and K. AKERBERG, Beitr. z. klin. d. Tuberk. **68**:527, 1928.

The Matéfy reaction was found a fair help in the prognosis of pulmonary tuberculosis. It is, however, less dependable than the sedimentation reaction.

MAX PINNER.

THE WHITE BLOOD CELL PICTURE IN THE VARIOUS TYPES OF TUBERCULOSIS ACCORDING TO NEUMANN. R. RUSSEW, Beitr. z. klin. d. Tuberk. **68**:539, 1928.

The amount of polynucleosis and of the shifting to the left indicates the severity of intoxication. Benign forms show lymphocytosis, not any or only slight shifting to the left, and normal amounts of eosinophils. The pathologic alterations of the blood picture are not an expression of the extent, the localization, or the pathogenetic type of tuberculosis, but of the amount of toxemia only.

MAX PINNER.

TREATMENT WITH SANOCRYSIN IN EXPERIMENTAL ANIMAL TUBERCULOSIS. L. LANGE, Beitr. z. klin. d. Tuberk. **68**:585, 1928.

Møllgaard's therapeutic experiments on cattle were repeated on eighteen animals. The treatment with sanocrysin and serum did not alter in any way the course of experimental tuberculosis in these animals as compared to control animals.

MAX PINNER.

CHRONIC PARATYPHOSUS SEPSIS AND PYEMIA. E. R. GRAWITZ, München. med. Wchnschr. **75**:560, 1928.

In the markedly enlarged spleen of a middle-aged woman, which had been removed surgically, there were multiple abscesses from which *B. paratyphosus* was isolated in pure culture. Following this a septic fever developed and *B. paratyphosus* was isolated from the circulating blood. Multiple abscesses formed and from these a similar organism was isolated. Recovery followed a prolonged illness.

E. F. HIRSCH.

EFFECT OF VARIOUS STRAINS OF STAPHYLOCOCCI ON GUINEA-PIGS. P. H. LONG, Ztschr. f. d. ges. Exper. Med. **58**:578, 1927.

The degree of phagocytosis in vitro (when exudative leukocytes of mice and normal rabbit serum were used) was determined for different strains of staphylococci (obtained from patients with abscesses, septicemia, osteomyelitis, etc.); the degree of phagocytosis was slight and similar in all strains. Phagocytosis in vivo (exudative leukocytes in the peritoneal cavity of guinea-pigs) likewise did not bring out any differences. Injections were made in thirty-six guinea-pigs with five different strains of staphylococci; the animals were killed after from seven to twelve days following the inoculation; in cultures from various organs, differences were not found. Previous "blocking" of the reticulo-endothelial system increased rather than decreased the resistance of guinea-pigs to various strains of staphylococci. Inoculation of guinea-pigs with living staphylococci (with or without previous "blocking" of the reticulo-endothelial system) increases, in vitro, the resistance of the erythrocytes of the animals to the hemolytic action of staphylotoxin.

B. LUCKÉ.

Immunology

RESPIRATORY IMMUNITY IN RABBITS. THE PRODUCTION OF HETEROPHILE ANTIBODY IN RABBITS BY INTRANASAL INFECTION WITH BACTERIUM LEPISEPTICUM. G. HOWARD BAILEY, Am. J. Hyg. **8**:398, 1928.

Intranasal infection or snuffles due to strains of *Bacterium lepisepticum* containing heterophil antigen incites the formation of antisheep hemolysin in rabbits. The same but less marked reactions occur in rabbits which are nasal carriers of such organisms. Individual and daily variations of antisheep hemolysin in the serums of normal rabbits could not account for the results obtained. The hemolytic antibodies incited in rabbits by intranasal infection with heterophil strains of *Bacterium lepisepticum* are absorbed from the serums in high concentration by the homologous micro-organism and also by the red cells of sheep. The hemolytic power of such an antiserum runs more or less directly parallel with the property of complement-fixation with the homologous strain of *Bacterium lepisepticum* or with lipoids derived from heterogenetic tissues. Negative results were obtained with lipoids from other tissues. Experiments with these serums and homologous and heterologous strains of *Bacterium lepisepticum* as antigens, before and after specific absorption with the red cells of sheep, indicate that the complement fixed by the heterophil bacterium is the sum of that fixed by the heterophil and non-heterophil fractions of the organism, the former alone being type specific. The marked local reactions following the intracutaneous injection of heterophil or non-heterophil strains of *Bacterium lepisepticum* into rabbits with snuffles due to this

organism are interpreted as specific allergic responses to this bacterium. The serums of rabbits immunized by intranasal infection with a heterophil strain of *Bacterium lepisepticum* show the property of primary antiserum toxicity for guinea-pigs.

AUTHOR'S SUMMARY.

THE WANING OF CUTANEOUS HYPERSENSITIVENESS TO TUBERCULIN AND THE RELATION OF TUBERCULO-IMMUNITY TO TUBERCULO-ALLERGY. HENRY STUART WILLIS, Am. Rev. Tuberc. **17**:240, 1928.

After infection with tubercle bacilli of low virulence, guinea-pigs exhibit a gradually declining cutaneous allergy as the infection subsides. As two years after infection, they fail to react to twice the usual reactive dose of tuberculin. At twenty-seven months after infection, one animal reacted positively to five times the ordinary reactive dose of tuberculin. Nothwithstanding this greatly reduced and practically absent allergy, such guinea-pigs, at thirty months after infection, were found to possess a high specific immunity to reinfection with virulent tubercle bacilli. The relations between tuberculo-immunity and tuberculo-allergy are discussed, particularly the question of possible latency of either allergy or immunity or of both, and the probable effect of reinfection on such latency. A scarcely detectable allergy in old and healing infection is immediately restored to old high levels by fresher infection. It is suggested that reinfection may similarly revive a waning tuberculo-immunity.

H. J. CORPER.

THE CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN. IX. FLORENCE B. SEIBERT, Am. Rev. Tuberc. **17**:394, 1928.

A protein-free fraction giving the specific tuberculin reaction could not be separated from the whole protein of tuberculin by fractional heat coagulation. Fractions coagulated at 50, 70, 80 to 90, 97 to 99 degrees (boiling) and 120 degrees (autoclaving), and even the final noncoagulable fraction, which also definitely contained some whole protein, all gave equally marked skin reactions to tuberculin, indicating that the specific biologic activity is not due to any particular fraction but rather accompanies all fractions in which the tuberculin protein is present. All fractions may therefore be derivatives of the same protein in varying stages of chemical change. These variations in coagulability are analogous to variations in solubility of different fractions of the same protein. The noncoagulable fraction has more primary toxicity than the coagulable fractions, as indicated by the lethal test, for normal as well as for tuberculous animals, although it does not give a more marked specific skin reaction in tuberculous animals. When one considers the tuberculin reaction, therefore, a certain primary toxicity of tuberculin must be recognized in addition to its well known capacity to elicit the specific tuberculin reaction in infected animals.

H. J. CORPER.

THE CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN: X. FLORENCE B. SEIBERT, Am. Rev. Tuberc. **17**:402, 1928.

The specifically active substance in tuberculin, which is responsible for the production of the skin reaction to tuberculin, is a water-soluble coagulable protein of the nature of an albumin, staining blue with methylene blue and containing the ordinary amino groups but not any carbohydrate, and crystallizable by the Hopkins methods at optimum p_H of 4.9. Even after fourteen crystallizations, the protein gave maximum skin reactions to tuberculin and caused a typical tuberculin atrophy in the testis of a tuberculous guinea-pig. A test made after ten crystallizations showed that less than half as much of the purified protein was required to produce an equally strong reaction as of the original fraction. The unit molecule of this crystallized protein is, however, unstable and easily becomes denatured. Such denaturization is recognized, first, by the facts that the protein will no longer

crystallize and that its solubility is changed and, second, by a loss in biologic activity. This instability explains the small yield of crystals and also the great losses in activity during the isolation of the protein.

H. J. CORPER.

PASSIVE TRANSFER OF THE SKIN REACTION TO HORSE SERUM. J. A. CLARKE, JR., and MAY G. GALLAGHER, J. Immunol. **15**:103, 1928.

About 0.1 cc. of serum from a person with a positive skin reaction to horse serum was injected into the skin of a normal person. In this way, a positive skin reaction to horse serum was transferred in five of seventeen patients sensitive to horse serum. All these patients were asthmatic. It is suggested that transfer of skin reaction in the way indicated may be of value in determining the degree of sensitiveness to horse serum.

PARENTERAL DENATURIZATION OF FOREIGN PROTEINS. W. H. MANWARING, H. D. MARINO and J. L. AZEVEDO, J. Immunol. **15**:109, 1928.

Titrations by means of rabbit precipitin indicate that horse proteins injected intravenously into normal dogs are retained apparently quantitatively in the circulation for at least ten days. Nevertheless, transfusions from these dogs into partially exsanguinated normal recipients show that these proteins are so altered by the seventh day as almost completely to lose their specific sensitizing power. It is conceivable that this parenteral denaturization is an initial stage in the formation of the specific antibodies.

AUTHORS' SUMMARY.

THE EFFECT OF RICINOLEATED VACCINE OF THE HEMOLYTIC STREPTOCOCCUS (SCARLET FEVER) ON ANIMALS. ANTHONY KOZLOWSKI, J. Immunol. **15**: 115, 1928.

When treated with sodium ricinoleate, the whole broth culture of the hemolytic streptococcus (scarlet fever) was more efficient in the immunization of mice than either broth toxin or bacterial cells. Sodium ricinoleate can be used in a soap-vaccine but only in small proportions as a disinfectant. The supposed detoxifying effect of sodium ricinoleate in a soap-vaccine or a soap-toxin may not depend on its physicochemical reactions with the bacterial products but is probably due to the destruction of animal tissues in the area in which the injection was made.

AUTHOR'S SUMMARY.

BACTERIOPHAGE AND PHAGOCYTOSIS. EFFECT ON RESISTANT AND DEAD BACTERIA. GEORGE H. SMITH, J. Immunol. **15**:125, 1928.

The exposure of susceptible, living bacteria to the homologous bacteriophage so alters these bacteria that they are more amenable to phagocytosis, and during such an exposure bacteriophage is withdrawn from the fluid in which it was originally present. The extent of the change to occur in the susceptible organisms is determined not only by the period of contact with bacteriophage but by the activity of the bacteriophage employed. Bacteria which have adsorbed bacteriophage and are thus rendered more amenable to phagocytosis continue to become even more susceptible to phagocytosis after the contact with bacteriophage is interrupted. Bacteria of the susceptible types which are killed prior to exposure to bacteriophage do not show an enhanced participation in phagocytosis, nor do they seem to deprive the bacteriophage suspension of its activity. The increased susceptibility toward phagocytosis derived from contact with bacteriophage is not destroyed by subsequent heating. As determined by the procedure here employed, organisms which are resistant, whether the resistance is natural or acquired, neither absorb bacteriophage from a suspension nor develop an increased tendency to undergo phagocytosis.

AUTHOR'S SUMMARY.

THE IMMUNOLOGICAL SIGNIFICANCE OF THE TUBERCULOUS TISSUE. L. DIENES, J. Immunol. **15**:141, 1928.

The introduction of antigens directly into the tuberculous lesions incites more antibody production than the subcutaneous and intravenous treatment of the tuberculous animal. Under appropriate conditions, only the injection of the antigens in the tuberculous lesions is effective. It is probable that the antibodies are formed in the tuberculous tissue and that the formation of the pathologic tissue is the cause of the increased antibody production after tuberculous infection.

AUTHOR'S SUMMARY.

THE ZONAL ACTION OF ANTISERUM IN PNEUMOCOCCUS INFECTIONS. HARRY SOBOTKA and MAE FRIEDLANDER, J. Immunol. **15**:175, 1927.

The prozone phenomenon is described and discussed in connection with the treatment of experimental pneumococcus septicemia with serum.

STUDIES ON THE "TOXINS" OF HEMOLYTIC STREPTOCOCCI. K. ANDO, K. KURAUCHI and K. OZAKI, J. Immunol. **15**:191 and 217, 1928.

Hemolytic streptococci isolated from pathologic foci, scarlatinal and non-scarlatinal, produce a toxic principle capable of evoking a cutaneous reaction in human subjects. Production of toxin varies considerably according to strains. Generally speaking, strains of hemolytic streptococci isolated from patients with scarlet fever and erysipelas have been found to produce a toxic principle capable of evoking a marked cutaneous reaction in a larger proportion of human subjects tested than in the case of the toxins produced by suppurative streptococci. The toxins produced by various strains isolated from the same pathologic conditions, e. g., scarlet fever, erysipelas or other suppurative lesions, may differ qualitatively when tested simultaneously on the same person. If, therefore, only a small number of persons were tested simultaneously with two monovalent toxins of *Streptococcus hemolyticus* from the same pathologic conditions, the reactions to both toxins might be entirely similar or entirely dissimilar to each other. This dissimilarity may become more marked, if scarlatinal, erysipelas and suppurative toxins were compared in their monovalent form. But, in comparing the scarlatinal, erysipelas and suppurative toxins by skin reaction, we employed polyvalent toxin and demonstrated that the reactions to them were similar to the majority of patients tested. This similarity was marked in the greatest degree in the case of scarlatinal and erysipelas toxin, and marked in a lesser degree in the case of erysipelas and suppurative toxin, while it was not marked in scarlatinal and suppurative toxin. The effectiveness of the toxin for both the Dick test and preventive immunization depends largely on the selection of suitable strains. It seems to be reasonable to use polyvalent toxin by mixing toxins of several strains which are most potent in strength and inclusiveness.

We have prepared three sorts of polyvalent toxins, scarlatinal, erysipelas and suppurative, by mixing several toxic preparations selected through skin reactions on human subjects and three sorts of antitoxin by immunization with these toxins. From the neutralization tests of polyvalent and monovalent toxins by these antitoxins on white pigs, the following conclusions may be drawn: Scarlatinal, erysipelas and suppurative antitoxic serums equally neutralize scarlatinal, erysipelas and suppurative toxins. The neutralizing action of these serums is most marked in the case of homologous toxin. Scarlatinal antitoxic serum prepared by us is more comprehensive in its neutralizing action than the erysipelas serum. The results of the neutralization tests with antiscarlatinal serum of monovalent toxins of various strains have shown that the majority of toxic preparations (thirty-two out of thirty-four strains), regardless of their sources, were neutralized with the exception of that produced by one erysipelas and one scarlatinal strain.

AUTHORS' SUMMARY.

THE ANTIGENIC PROPERTIES OF VACCINIA AND RABIES VIRUS. E. W. SCHULTZ, L. T. BULLOCK and F. LAWRENCE, J. Immunol. **15**:243 and 265, 1928.

No evidence of specific complement fixation could be demonstrated when immune serums, produced in rabbits with pure vaccinia brain-virus, were tested against antigens prepared from the lesions of cutaneous vaccinia or against brain-virus antigens. No specific complement fixation occurred when immune serums, produced with cutaneous vaccinia virus, were tested against antigens prepared from brain-virus. Although the latter serums, fixed complement in the presence of antigens prepared from cutaneous vaccinia pulp, an almost equivalent degree of complement fixation was observed in the presence of antigens prepared from bacteria cultured from this pulp. Antiserums produced against bacteria, harvested from the pulp of cutaneous vaccinia lesions, fixed complement, in the presence of antigens prepared from cutaneous vaccinia lesions. No evidence for the presence of specific precipitins in the two kinds of vaccinia immune serums could be elicited. Precipitates, which did not occur in certain cases, were shown to be due to unspecific reactions. Virulicidal antibodies were easily demonstrable in all the immune serums examined for this property.

Evidence for the presence of specific complement fixing antibodies against the virus of rabies was not found in the serum of rabbits which had been immunized in various ways with fixed virus brains. These immune serums also failed to present any evidence of specific precipitins. Rabicidal antibodies were demonstrated in all of the immune serums tested for this property.

AUTHORS' SUMMARY.

THE EFFECT OF CHLOROFORM ON THE IMMUNIZING ACTION OF VACCINE VIRUS. F. DURAN-REYNALS, J. Immunol. **15**:283, 1928.

When vaccine virus was so far inactivated by chloroform that eruptions did not result from the intradermal injection of large doses, no immunity was induced in the animals. When the chloroform virus produced any lesion whatever, the rabbits subsequently proved immune when tested by a second injection of untreated virus. These experiments support the general idea that inactivated vaccine virus is incapable of giving rise to immunity.

AUTHOR'S SUMMARY.

PASTEURELLA AVICIDA VACCINATION BY THE ORAL, SUBCUTANEOUS AND INTRAVENOUS METHOD. LA VERNE BARNES, J. Immunol. **15**:289, 1928.

Intravenous vaccination is superior to the oral and subcutaneous methods in stimulating the production of agglutinins for *Pastuerella avicida* in chickens and rabbits. The subcutaneous method is superior to the oral method in this respect. Greater resistance to intravenous injections of *Pastuerella avicida* is produced by intravenous vaccination than by the oral and subcutaneous methods. It is probable that, from the standpoint of local immunity, the method of application of vaccine should correspond to the portal of entry of the infecting organism. The results obtained in this series of experiments do not disagree with Besredka's theory of local immunity.

AUTHOR'S SUMMARY.

EXPERIMENTS ON THE VIRUS OF FOWL PLAGUE. CHARLES TODD, Brit. J. Exper. Path. **9**:101, 1928.

Attempts to immunize fowls against fowl plague with heated virulent materials (blood, spleen, etc.) and with the formalinized vaccine were unsuccessful, but a solid immunity to the disease was produced by the use of a phenol glycerine vaccine prepared from the liver of birds dead of the disease. Birds thus immunized to the English strain were found to be immune also to various other strains (Dutch, French and German).

S. D. SIMON.

FURTHER NOTES ON SPONTANEOUS AGGLUTINATION OF BACTERIA. P. BRUCE WHITE, J. Path. & Bact. **31**:423, 1928.

The following forms of unspecific agglutination have been determined: unspecific agglutination by electrolytes determined by the bacterial lipoids and following on loss of soluble specific substance (the salt-agglutinability of rough variants); unspecific agglutination by electrolytes determined by sheer intensity of "lipoid" influence (the salt-agglutinability of certain smooth races); unspecific agglutination by electrolytes following denaturation of the bacterial protein (the special salt-agglutinability of heated rough variants); unspecific agglutination in the presence of serum due to reaction therewith of certain lipoid constituents of the bacilli (the serum-agglutination of certain rough variants).

AUTHOR'S SUMMARY.

THE IMMUNITY INDEX METHOD OF TESTING ANTIGENIC VALUES. A. T. GLENNY and HILDA WADDINGTON, J. Path. & Bact. **31**:403, 1928.

Guinea-pigs receiving weekly injection of Schick toxin may become Schick negative at the eighth injection. Guinea-pigs receiving weekly injections of Schick toxin are more readily immunized when the series of injections is commenced in the summer or early autumn. The general condition of animals affects their rate of immunization. The immunity index method has been used to demonstrate the following: that qualitative differences exist between different batches of toxoid depending on amount of precipitable material, types of broth used in preparation, amount of formaldehyde used, presence or absence of phenol; that toxoid precipitated at p_H 0.2 is still antigenic; that ricinoleate toxoid is antigenic: that the addition of potassium alum or of turpentine or toluol increases the antigenic efficiency of toxoid; that the antigenic efficiency of toxin-antitoxin and of toxoid-antitoxin floccules is increased by heating the floccules to 70 C. for one hour; that immunity response to one antigen may be lowered by simultaneous response to other antigens; that dye-blockaded guinea-pigs show little response, and that dilution of toxin-antitoxin mixtures causes dissociation.

AUTHORS' SUMMARY.

THE LYMPHATIC STAGE OF TUBERCULOUS INFECTION IN CATTLE. A. CALMETTE and C. GUÉRIN, Ann. de l'inst. Pasteur **42**:175, 1928.

It is necessary to practice vaccination with BCG in the first days following birth, at the latest, before the expiration of the second week. Calves born in an infected stable should be removed from such environment for a month following vaccination (until a state of resistance is established); during this period, care should be used in protecting the animals from infected milk.

AUTHORS' CONCLUSIONS.

ANTIVIRUS THERAPY AND LOCAL ANESTHESIA. S. NAKAGAWA, Ann. de l'inst. Pasteur **42**:196, 1928.

Three series of guinea-pigs were used. Local anesthesia was produced with a 0.5 per cent procaine hydrochloride solution, following which a "streptococcus antivirus" was injected. Immunity was tested by the injection of virulent streptococci. Local anesthesia inhibited the preventive action of the antivirus to some extent as compared with controls, the inhibition being limited to the region affected by the procaine hydrochloride.

M. S. MARSHALL.

CUTANEOUS IMMUNIZATION OF THE GUINEA-PIG AGAINST ANTHRAX. M. N. SOLOVIEFF, Ann. l'inst. Pasteur **42**:200, 1928.

Successful immunization of guinea-pigs against anthrax was secured, the two Cienkovsky vaccines being injected into the skin. Since the serum of immunized

animals did not have power to protect, the immunity would appear to be local. With the Besredka technic, the first vaccine is insufficient to protect against the second, which may account for the failures reported by some other authors.

M. S. MARSHALL.

LOCAL IMMUNIZATION AGAINST SCARLET FEVER. G. D. BELONOVSKY and A. A. MILLER, Ann. de l'inst. Pasteur **42**:206, 1928.

Following the principles of the Besredka technic, the authors first attempted, with apparent success, the immunization of rabbits against cobra venom by means of spraying the pharyngeal region with solutions of venom of increasing concentration. They then turned to scarlet fever streptococcus toxin, using a spray on the conjunctiva of rabbits, previously made sensitive with bile. This also proved successful as a demonstration of local immunization, and was followed by experiments on human volunteers. Treatment proved innocuous, and vaccination by spraying the pharyngeal region of more than 8,000 children has been practiced. Although the data are too incomplete to lead to unequivocal conclusions, the immunization seems to be practically complete for a period of four months, after which there is a gradual return to the susceptible condition.

M. S. MARSHALL.

VACCINATION WITH THE WEEKS BACILLUS. PAUL DURAND and UGO LUMBROSO, Arch. de l'Inst. Pasteur de Tunis **16**:365, 1927.

A polyvalent vaccine, composed of strains of the Weeks bacillus varying serologically, was used on a number of children of school age without ill effects. An appreciable reduction in the frequency of the occurrence of this organism was effected, both in trachomatous and in nontrachomatous children. Patients with trachoma seemed to be benefited by the vaccine even more than nontrachomatous children, owing to the frequent association (in Tunis) of infection with the Weeks bacillus and trachoma.

M. S. MARSHALL.

EXPERIMENTAL B C G VACCINATION. A. BOCCHINE, Pediatria **36**:169, 1928.

In a series of rabbits, the intravenous injection of B C G in a maximal dose of 30 mg. caused serious specific lesions and did not protect against subsequent virulent infection. In fact, all the animals died with signs of general tuberculosis from one to three months after inoculation with virulent tubercle bacilli. Four months after vaccination and forty-eight days after the virulent inoculation, one of the rabbits gave birth to a premature fetus, which was apparently normal. Intraperitoneal inoculation of parts of its organs, however, caused the death of a guinea-pig twenty-six days after inoculation, with signs of general tuberculosis.

PRACTICAL APPLICATION OF THE SEROREACTION ACCORDING TO LEHMANN-FACIUS AND LOESCHCKE, FOR THE DEMONSTRATION OF PRECIPITATING ANTIBODIES IN ACTIVE TUBERCULOSIS. R. STEINERT, Beitr. z. Klin. d. Tuberk. **68**:545, 1928.

The result of the application of this reaction to 200 tuberculous patients yielded encouraging but not strictly dependable results.

MAX PINNER.

EXPERIENCES WITH NEUBERG-KLOPSTOCK'S TUBERCULOSIS ANTIGEN. K. SIEGFRIED, Beitr. z. Klin. d. Tuberk. **68**:558, 1928.

Neuberg-Klopstock's antigen was used in complement fixation tests in about 200 cases of tuberculosis. A large percentage of patients reacted positively. The reaction is positive regardless of the clinical activity of the lesion. In many cases showing positive reactions, the sedimentation reaction was normal, and in 3 per cent of the cases showing positive reactions even the Pirquet reaction was negative.

MAX PINNER.

SENSITIVENESS TO GLYCERIN BROTH. G. DEMOHN and H. FERNBACH, Beitr. z. Klin. d. Tuberk. **67**:649, 1927.

Guinea-pigs made allergic to tuberculin by the injection of live or dead tubercle bacilli are not at all, or only slightly, sensitive to concentrated glycerin broth. Continuous intracutaneous treatment with this broth does not increase the local sensitiveness. The acute reaction after the intravenous injection of old tuberculin or glycerin broth is identical for both substances, and is undoubtedly due to nonspecific substances contained in the broth.

MAX PINNER.

ERRORS IN THE STUDY OF HEREDITY OF BLOOD GROUPS. L. LATTES, Verhandl. d. ständigen Kommission. f. Blutgruppenforsch. **1**:13, 1928.

Lattes discusses errors in blood grouping due to faulty technic and the bearing such errors may have on the alternative hypotheses of von Dungern and Hirszfeld and of Bernstein. He contributes new data on the blood groups of mothers and children, in which mothers of group O had children of groups O, A and B, but never of AB, while mothers of group AB had children of groups A and B, but not of O or AB. These results confirm Bernstein's hypothesis and are contrary to the hypothesis of von Dungern and Hirszfeld.

L. H. SNYDER.

BLOOD GROUPS AND ANTHROPOLOGY. B. WISCHNEWSKY, Verhandl. d. ständigen Kommission. f. Blutgruppenforsch. **1**:13, 1928.

Wischnewsky reviews the literature on blood grouping from an anthropologic standpoint. Every physician who does any grouping can add to the total knowledge in this field. It is important to study mixed races, especially when both components may also be studied in their original form. Of outstanding importance is the question of the relations of the blood groups to morphologic, physiologic and pathologic constitution. A coöperative program between physicians and anthropologists is urged.

L. H. SNYDER.

THE NEW BIOCHEMIC RACE INDEX. A. A. MELKICH, Verhandl. d. ständigen Kommission of Blutgruppenforsch. **1**:32, 1928.

The author presents a new "biochemical race index" to supplant those of Hirszfeld and Wischnewsky. The new formula is as follows:

$$\text{Index} = \frac{O + A}{B + AB}$$

This index takes into account all four groups and in certain instances gives different indexes for races having the same index on the Hirszfeld system.

L. H. SNYDER.

THE CHANGES IN THE ISO-AGGLUTINATION PROPERTIES OF THE BLOOD IN FATIGUE. M. DENISSENKO and M. SCHEINERMANN, Verhandl. d. ständigen Kommission f. Blutgruppenforsch. **1**:52, 1928.

By titration of test serums before and after exertion on the part of the subjects, the authors found that the agglutinophilic capacity of erythrocytes is increased from 50 to 150 per cent by physical fatigue.

L. H. SNYDER.

THE BIOLOGIC RACE INDEX OF THE GERMAN COLONISTS IN UKRAINE. W. RUBASCHKIN and S. PAULI, Verhandl. d. ständigen Kommission f. Blutgruppenforsch. **1**:65, 1928.

The blood groups of 268 German colonists in Ukraine were as follows: group O, 31 per cent (83); group A, 47 per cent (126); group B, 16.8 per cent (45) and group AB, 5.2 per cent (14).

L. H. SNYDER.

THE BLOOD GROUPS OF PATIENTS WITH MALARIA. L. I. LEISERMANN, Verhandl. d. ständigen Kommission f. Blutgruppenforsch. **1**:67, 1928.

The blood groups of 252 patients with malaria were normally distributed, and inconsistency between the reaction of the erythrocytes and the corresponding serum reaction was not found in any case.

L. H. SNYDER.

INHERITANCE OF BLOOD GROUPS. T. FURUHATA, Verhandl. d. ständigen Kommission f. Blutgruppenforsch. **1**:69, 1928.

Furuhata reviews the literature on the heredity of the blood groups, presenting tables which summarize the work done by various authors along this line. He presents his own hypothesis of the inheritance of the groups, which is essentially the same as that of Bernstein but which takes into account the agglutinins as well as the agglutinogens. The hypothesis is in effect one of complete linkage. Data on 958 families studied by the author and his associates are presented. The genetic formulas of the four groups on Furuhata's hypothesis are as follows:

Group O = (ab) (ab)
Group A = (Ab) (ab) or (Ab) (Ab)
Group B = (aB) (ab) or (aB) (aB)
Group AB = (Ab) (aB)

Tables showing the results of all possible combinations of the four groups are given.

L. H. SNYDER.

EXPERIMENTS WITH THE B C G STRAIN OF CALMETTE. H. CHIARI, E. NOBEL and A. SOLÉ, Ztschr. f. Tuberk. **50**:24, 1928.

Guinea-pigs were infected with B C G bacilli intraperitoneally in the dosage of 1 to 80 mg., and examined from 15 to 174 days after the infection. The majority of these animals showed tuberculous lesions. In three of twenty-six animals it was possible to recover the organism in cultures. A few animals are reported to have died of tuberculosis. Whatever immunity is produced by B C G is due to a tuberculous infection. The experiments yielded good evidence for Calmette's claim that most of the lesions produced are benign and heal.

MAX PINNER.

IMMUNIZATION OF THE NEW-BORN AGAINST TUBERCULOSIS BY B C G. REPLY TO THE ARTICLE BY H. CHIARI, E. NOBEL and A. SOLÉ. A. CALMETTE, Ztschr. f. Tuberk. **50**:38, 1928.

The experimental observations of Chiari and his associates must be due to an experimental error, since the avirulence of the strain has been demonstrated in thousands of animals. The intestinal resorption of the bacilli in young animals is proved by the subsequent polyadenitis. Sensitization against tuberculin occurs only in those exceptional cases in which the B C G bacilli produce follicular lesions in the lymphatic organs; such lesions always heal. The virulence of the organism is proved beyond doubt by its wide application in human beings.

MAX PINNER.

EXPERIMENTAL STUDIES ON GUINEA-PIGS AND RABBITS REGARDING THE IMMUNIZATION WITH B C G. B. LANGE and K. LYDTIN, Ztschr. f. Tuberk. **50**:45, 1928.

The inoculation of large amounts of B C G into guinea-pigs and rabbits produced a tuberculous infection. In the majority of the animals this infection was definitely benign, i. e., progressive lesions never developed, and the local lesions healed. Only those animals which received a large dosage intravenously were definitely harmed. An increase in the virulence could not be obtained by animal

passage. Most animals which received the inoculation subcutaneously, intracutaneously, intraperitoneally and intravenously developed typical tuberculin allergy. The animals which were treated per os or by inhalation developed the allergy less frequently. Tuberculous tissue was found at the site of the injection in the animals which were treated parenterally, while definite tuberculous lesions were not demonstrable after natural infection. The immunity produced was definite but was quantitatively limited. These studies essentially substantiated Calmette's claims.

MAX PINNER.

EXPERIMENTS IN THE IMMUNIZATION OF GUINEA-PIGS AGAINST TUBERCULOSIS. G. SCHRÖDER, Ztschr. f. Tuberk. **50**:61, 1928.

Guinea-pigs were immunized by a vaccine prepared by seeding tubercle bacilli into thymus tissue. Animals so treated lived longer, gained more in weight and developed more benign types of tuberculosis after the infection with virulent bacilli than did the control animals.

MAX PINNER.

IMMUNIZATION OF THE NEW-BORN AGAINST TUBERCULOSIS WITH BCG. A. CALMETTE, Ztschr. f. Tuberk. **50**:121, 1928.

The technic and the theoretical foundations of this method by immunization are reiterated. It is emphasized that immunized children should not be exposed to infection for the first months following immunization, since it takes about one month until actual immunity develops. From the first of July, 1924, to the first of September, 1927, 52,777 new-born infants have been immunized. Among 3,808 children living in tuberculous surroundings who were immunized during the last year, the general mortality was 3.1 per cent, while in children of the same age who were not treated and who did and did not come in contact with tuberculous persons, it was 8.5 per cent in France. The mortality of tuberculosis of the immunized children was 1.5 per cent; for the nonimmunized ones, 24 per cent. Out of 1,941 immunized children living in contact with tuberculous persons, of those between the ages of 1 and 3½ years, 1.2 per cent died and 0.2 per cent of these died of tuberculosis. The general mortality of the same age group in the entire population was 1.6 per cent, and the tuberculosis mortality was 0.4 per cent. Immunity seems to last at least five years. The good general health of the children immunized five years ago proves that the BCG bacilli remain avirulent in the organism.

MAX PINNER.

Tumors

CENTRIOLES AND THE HISTOGENESIS OF THE MYOFIBRIAL IN TUMORS OF STRIATED-MUSCLE ORIGIN. S. BURT WOLBACH, Anat. Record **37**:255, 1928.

1. This is a study of the cytologic details accompanying the differentiation of the cells in growing tumors of striated muscle, one from the heart and one from skeletal muscle. In both tumors there were cells in mitosis, cells with completely differentiated myofibrils and cells in intermediate stages of development.

2. The assumption is made that the tumor cells in their differentiation have recapitulated normal embryologic sequences.

3. Arrangement of the cells of those tumors in order of increasing complexity of detail suggest the following sequence: (1) multiplication of centrioles; (2) dispersion of centrioles in the cytoplasm; (3) formation of fibrils from the cytoplasm between the granules of centriole origin.

The fibrillary material of cytoplasmic origin contracts to form the Z band (telophragma), the granules of centriole origin give rise to dark disc or Q band.

AUTHOR'S SUMMARY.

A Further Study of Gye's Hypothesis on the Etiology of Malignant Tumors. John A. Kolmer and Malcolm J. Harkins, J. Cancer Research **11**:217, 1927.

Gye affirms that all tumors provide a virus which is universal and unable alone to produce a new growth; a second substance is necessary—a "specific factor" which is obtained from tumor extracts and which enables the virus to infect. The experiments related in this study corroborate the previous report by Harkins, Schamberg, Kolmer and Kast (*J. Cancer Research* **10**:66, 1926), in which was demonstrated the difficulty, or rather the impossibility, of preparing a noninfectious "specific factor" unless a concentration of chloroform greater than that stated by Gye was used. In this investigation as in the previous one, Kolmer and his associates failed to confirm Gye's hypothesis on the etiology of malignant new growths.

B. M Fried.

Culture in Vitro of Human Tumors. E. Gioja, Tumori **2**:205, 1928.

The author has made tissue cultures of the following materials: (1) a hyperplastic lymph node; (2) a metastatic carcinoma of the breast in a lymph node; (3) a metastatic carcinoma of the stomach in a lymph node; (4) a recurrent carcinoma of the parotid gland; (5) a bone metastasis of a round cell sarcoma; (6) a spindle cell sarcoma of the neck; (7) a periosteal round cell sarcoma of the humerus, and (8) a fibrosarcoma from a case of von Recklinghausen's disease. He gives numerous photomicrographs of the original tumors and of the growths obtained. The most vigorous development was observed in the spindle cell sarcoma of the neck. Gioja comes to the following general conclusions: The most favorable conditions for the development of tumor material in a human being are a delicate coagulum and an admixture of a third part of human embryonic extract. The period of incubation is always over twenty-four hours and sometimes from forty-eight to seventy-two hours. The growth of the culture is not, as a rule, as vigorous as that of embryonal tissue and of tumors in animals. The period of development or "fertile stage" varies a great deal, but is approximately from three to ten days. Following this the culture remains stationary and the cells become necrotic. Transfers should probably be made in the beginning of the fertile stage. In one case, cells could still be stained after eighteen days. The period of growth is somewhat longer in sarcomas than in carcinomas. The central part of the transplant undergoes necrosis; growth takes place only from the margins. In the cultures of carcinoma the cells of the stroma as well as the epithelial cells almost always show signs of proliferation. In the cultures of a spindle-shaped sarcoma, the cells retained their spindle shape until the eleventh day when they suddenly changed into rounded elements; this was probably a sign of involution. One reason for the frequent lack of success in obtaining growths is the fact that the piece selected for culture is dead, although grossly it may not appear to be so. The author has not observed any difference in growth in the plasma of persons having the tumors and in that of indifferently selected persons.

W. Ophüls.

On Adenoma of the Islands of the Pancreas. C. Natali, Tumori **2**:244, 1928.

The author reports the occurrence of an insular adenoma in a patient, who in addition, had an adenocarcinoma of the stomach with extensive metastases in the lymph nodes, the liver and the right pleura. He gives a list of the cases which have been published so far and discusses the subject under the following headings: certain inconstant peculiarities in the structure of insuloma, the origin of the islets, genetic hypotheses in regard to insular adenoma, hypertrophy or blastoma (?), relation to diabetes, hamartomatous origin of insuloma, attempt at interpretation and classification of insular hamartoma.

W. Ophüls.

RECENT CARCINOMA REACTIONS AND THEIR CLINICAL VALUE. K. ATZERODT, Klin. Wchnschr. **7**:1077, 1928.

Neither the albumin reaction (Suranyi) nor the indicator test (Gross), alone or together, are of value for the diagnosis of early stages of carcinoma.

AUTHOR'S SUMMARY.

Medicolegal Pathology

A MEDICOLEGAL STUDY OF THE CALCUTTA RIOTS OF 1926. J. C. DE, Indian M. Gaz. **62**:479, 1927.

In three riots, 141 people were killed and 1,201 were injured; 124 postmortem examinations were performed. During these examinations, 511 wounds were found, only 19 of which were due to bullets. There were 208 cuts and stab wounds, 190 lacerated wounds and 94 contusions. The largest number of wounds in any single body was 17, and 24 bodies had only 1 wound each. Many tables are given and good records are included of the amounts of blood found in body cavities from stab wounds of the heart and large blood vessels. No children, women or very old men were killed. Many of the persons whose bodies were examined died in hospitals, subsequent to the riots. Each riot lasted about a week.

E. R. LE COUNT.

THE COLLAR OF STAINING ABOUT BULLET WOUNDS OF ENTRANCE. CHAVIGNY, Ann. de méd lég. **8**:126, 1928.

TRANSPORTATION OF DUST BY CONICO-CYLINDRICAL BULLETS. GENERAL JOURNEE and DR. PIÉDELIÈVRE, ibid., p. 128.

The conclusions of these students of missile wounds are complementary. Chavigny did not find any stains about entrance wounds made with polished steel bullets fired with compressed carbon dioxide from carefully cleaned gun barrels. And with appropriate apparatus for registering the temperature, he concluded that the stain about entrance wounds on the first sheets of books into which bullets were fired with powder from about 650 feet (200 meters) was not due to heat, for the temperature registered by appropriate apparatus was not above 80 C. The ingenuity of experimentation by Piédelièvre in studying bullet wounds has already been commented on in these abstracts (*Ann. de méd. lég.* **5**:735, 1928).

He now describes how the sides of the wounds, more or less conical according to the velocity of the bullets, are stained red with eosin when minute dimpling depressions are made in the tips of bullets and filled level with eosin before firing. A little of the stain probably is spilled when the bullets begin to revolve from rifling (grooving) of the inside of the gun barrels. The revolutions were from 690 to 2,330 per second, and neither revolutions nor velocity interfered with the staining due to the eosin.

The bullets were fired from about 43 feet (13 meters) into putty which they penetrated a distance of 40 cm. A sheet of brown paper with its back surface colored blue was placed on a frame of wood 20 cm. in front of the putty. Different weapons were used, and different charges of powder. The eosin in the small depression made in the tips of the bullets was sometimes dry, and other times mixed with petrolatum. Sometimes a faint red stain was found about the bullet-hole in the brittle paper ahead of the putty, but the putty was always stained, at both the sides and the ends of the bullet paths. Blue was not carried into the putty. The staining of the putty was not the same with different charges and weapons, but the differences were simply in degree. These experiments demonstrate that particles of dust, lead and powder may easily be carried ahead of bullets for great distances.

Apparently, the revolutions of the bullets about their long axes, instead of scattering the dust in all directions, collect it into more or less compact masses in a manner such as that in which undissolved particles are gathered in the center of the bottom of a glass when fluid is revolved in an endeavor to dissolve a salt. Held there ahead of the bullet by its rapid revolutions, the dust is literally centrifugalized and carried on so as to stain the skin which, unlike brittle paper, is elastic and is driven in by the bullet before penetration takes place. The "collarette," therefore, is a stain by dust, in which particles of lead, carbon, unburned powder and rust predominate. Into the whirling vortex just in front of the bullet, doubtless particles of dust from the air are also drawn.

Some confirmation that a centrifugalizing force is operative was also secured by putting glass ampules filled with colored fluid in the minute cup-shaped excavations in the front end of the bullets. From some of the guinea-pigs killed by such bullets, the glass capsules were recovered unbroken.

E. R. Le Count.

Chronology in Legal Medicine. Chavigny and Simonin, Ann. de méd. lég. **8**:117, 1928.

It is often necessary to decide, if possible, which of two injuries was inflicted first. For example, two men attack a third who receives wounds delivered by each assailant, that are generally regarded as fatal or mortal. If the assaulters are tried separately, or if only one comes to trial, precise information is required about the wounds. The increase in accidents, many of them fatal, from motor-driven street vehicles, has brought with it many complicated problems of liability. Many of these arise from accidents in which two or more vehicles take part. One automobile or truck may kill a pedestrian and another run over or injure the corpse, or the first injure and the second kill.

One machine may strike a second so as to injure or kill some one outside both, and the injured person may or may not be on foot. If the person is knocked unconscious, another automobile may produce additional injuries, or subsequent injuries may be sustained by the machine which knocked the person unconscious. In a measure, the difficulty of ascertaining the priority of this or that wound, and of determining which, if any, are postmortem, have been matters of critical study for a long time in the bodies of persons killed by a number of bullets of different calibers, and in bodies run over by trains subsequent to murder.

These two French writers of the Faculty of Legal Medicine in Strasbourg report the conditions found by them in several bodies with injuries successively made, some after death. Particular emphasis is laid on the changes in wounds which are due to tears of the heart or large blood vessels, through which sufficient blood pours to greatly lessen bleeding from wounds elsewhere. A similar trouble is encountered in tracing the paths of bullets, when others have previously passed through the heart.

E. R. Le Count.

Roentgenoscopy in Medicolegal Work. J. Belot, Ann. de méd. lég. **8**:132, 1928.

In discussing failure to find foreign bodies, Belot mentions the value and use of x-ray examinations of the entire body for bullets, as advocated by Balthazand; he also mentions three cases of foreign bodies loose in the cavities of the heart and the necessity of speeding up the time of exposure in photographing them because they revolved rapidly in orbits owing to the force of the blood currents.

E. R. Le Count.

Treatment of Electrocution. M. De Saet, Ann. de méd. lég. **8**:134, 1928.

The inhalation of oxygen plus 5 per cent carbon dioxide, the injection of pure oxygen subcutaneously and intraperitoneally and prolonged artificial respiration

reanimated rabbits apparently dead from electrocution with voltages as low as 250 and as high as 10,000. An extreme dilatation of minute veins in the conjunctivae and ears was noted; with the maximum dilatation hemorrhages occurred. These happened during the first five or ten seconds of subjection to the current. When the heart was examined quickly in animals apparently dead from such electrocution, it responded to irritation by beating and was often found undergoing fibrillary twitching. Nothing abnormal was observed in the animals brought back to life. Death is simply counterfeited when the passage of the current has not been too long.

E. R. Le Count.

The Relation Between Pulmonary Tuberculosis and Bullet Wounds of the Lungs. A. Leipold, Deutsche Ztschr. f. d. ges. genichtl. Med., **11**:169, 1928.

During the thirteen years, 1914-1927, studies were made in the Barmbeck Hospital in Hamburg of 160 patients with fresh bullet wounds and of ten with old bullet wounds of the lungs. One patient developed phthisis during treatment in the hospital for wounds of the left hand and arm. It was concluded that the tuberculosis was due to lessened freedom of respiration caused by immobilization of the left arm. Open pulmonary tuberculosis was present in five of the ten patients with old wounds, but a causal relation between wound and disease was found in only one of these.

Twenty-eight of the 170 patients were carefully examined some time after recovery from the wounds, roentgenoscopy being included in the examination; a third patient with the causal relationship was found in this group. A fourth with phthisis from such wounds of the lungs was discovered by inquiries made to fifty-three others of the 170 who had left the hospital and were no longer available for examination. This is indeed a small number. Wounds of lungs from the missiles of fire arms and warfare are rarely followed by tuberculosis. From the records of the medical literature, Leipold found the incidence to be 3.3 per cent of a total of 1,522 cases, an infrequency corresponding closely with his own observations.

E. R. Le Count.

Cadavers from the Rhein. Berg, Deutsche Ztschr. f. d. ges. gerichtl. Med. **11**:278, 1928.

Düsseldorf is about 25 miles by rail down the Rhein from Cologne, and about 32 by the river. Between the two cities the river is one fifth of a mile wide; it has rocky shores, a rock or gravel bed and a fairly swift current. There are some bathing beaches where sand and mire have accumulated between stone piers built out at right angles from the shores. During his twenty-one years of experience with the medicolegal work at Düsseldorf, Berg has examined hundreds of bodies from the river. They make up a large part of those examined. In 1926, for example, forty-one bodies of a total of 203 examined for medicolegal inquiries were from the river. He has noted that the bodies are of two sorts, those which come from Cologne, and others from the immediate vicinity of Düsseldorf. Those floating down from Cologne have abrasions of the forehead, backs of the hands, outsides of the forearms, front of each knee and dorsal surfaces of the toes. When raiment covers these parts it is torn or worn off. Such alterations are caused by the rough river bed, for the body is borne along by the current face down and head first, the head bent forward on the trunk, and the extremities slightly bent. The bodies of those drowned near by or at the bathing beaches do not possess such abrasions. Other tears, usually deeper and more mutilating, are caused by the blades of boat propellers or other objects of river traffic. In the cold months of the year, when floatation from putrefactive gases does not occur, bodies may take one or two months for the passage. The body of a plump young woman drowned at Cologne when a row boat capsized

was recovered at Düsseldorf twenty-one and a half hours later uninjured. It had been carried down swiftly by the current. When lightly clad, the bodies do not rise until decomposition is advanced. The current keeps them down.

Bodies without injuries are rare, and adipocere bodies are still more infrequent. Berg encountered this waxlike transformation only in bodies which had become entangled in some way and anchored to the bottom. The change to adipocere required three months in the Rhein. In the Danube at Vienna, it may occur in five weeks. He disputes the opinion held by some that the bodies of women float face up in a current. The clothing is torn off the bodies of women coming from Cologne more commonly than from those of men. He is profoundly impressed with the need for thorough examination of the bodies removed from the Rhein, because evidence of injury or of death from criminal violence before the bodies have entered the water have often been found, and convictions for the crimes are rarely obtained. Escape from the penalties for murder apparently is rendered highly likely by the casting of injured or dead victims into the Rhein.

The bodies of persons who have committed suicide frequently are weighted with stone or metal, the hands and feet tied, or the mouth and nostrils tightly covered. In the bodies of adults, contusions are often still demonstrable after two months, and in spite of considerable postmortem decomposition. In the bodies of infants, such injuries disappear more quickly in the water. This report by Berg takes rank with the careful observations of bodies recovered from the Alpine lakes (Ipsen, Merkel) and those from the Danube (Haberda). In all three localities, the temperature of the water, absence or not of current and vegetation and other factors result in different alterations.

E. R. Le Count.

Preservation of Proofs of the Scattering of Powder Stains. Dyrenfurth and W. Weimann, Deutsche Ztschr. f. d. ges. gerichtl. Med. **11**:288, 1928.

It is essential that records suitable as evidence be made and preserved of the distribution of powder marks on the clothing and the skin. The distance of the muzzle of the weapon from the wound may be determined by experiments which reproduce a scattering similar to that under investigation. By means of an adhesive solution called mastisol which is spread on white paper and applied closely to clothing or to the skin, a proof-sheet is obtained of the location of the powder marks about the entrance wounds of bullets.

Particles of powder come away when the sheet is removed and remain fast on the sheet. The solvent for the gummy substance evaporates. When desired, bits of powder may be removed from the sheet and examined chemically. Collodion, putty, paraffin and mixtures of glycerol and gelatin have also been used as adhesive to remove the powder or to secure imprints of the location and dissemination of the wounds made by grains of powder. Such sheets to which the powder adheres may be introduced in court, together with those obtained by appropriate experiments with ammunition and weapons identical with those employed in the shooting.

E. R. Le Count.

Peculiar Cadaveric Livores. Berg, Deutsche Ztschr. f. d. ges. gerichtl. Med. **11**:317, 1928.

On the buttocks and the back of the trunk and thighs, symmetrical straight or slightly curved parallel discolorations, varying from red to purple, were found in the skin of the body of a woman who died from air embolism on the operating table in the house of an abortionist. They were finally explained by post mortem settling and clotting of the blood in folds of skin made by the clothing when the body was carried by the abortionist and the woman's son to where it was subsequently found.

E. R. Le Count.

Technical

A Description of a Simple Laboratory Apparatus for Obtaining Accurate Tracings of Objects. Alberta Doyle Innes, Anat. Record **36**:195, 1927.

This apparatus was devised for the purpose of making rapid and accurate drawings of anatomic objects. Two sheets of glass are clamped one above the other, the space between the two sheets and that between the lower one and the table being about 12 inches (30.48 cm.). The object to be drawn is placed on the upper glass. Above it a piece of white cardboard is clamped horizontally to act as a reflector. The object is illumined by an electric lamp, clamped to a retort stand, which can be shifted as needed to light all sides of the object. The lower sheet of glass acts as a mirror. On it a cross is drawn with India ink. This cross must be fixed on one particular point of the object to insure accuracy in drawing. The paper on which the drawing is made is placed under the lower sheet of glass. Any thin, dark, tracing-paper can be used, but the best results are obtained with gray translucent graph paper.

The Kahn Test in Primary Syphilis. J. C. Willett and Nathan Nagle, J. A. M. A. **90**:1189, 1928.

The Kahn test gave positive results in 80 per cent, and examination with the dark-field in 60.95 per cent of a group of patients in all but four of whom there were primary lesions less than twenty-eight days old.

Blood Group Classifications. James A. Kennedy, J. A. M. A. **90**:1323, 1928.

The Moss classification is in use in 72 per cent of 375 hospitals answering a questionnaire. More than one half of the persons who make tests for blood grouping appear unfavorable to the adoption of Landsteiner's O, A, B and A B systems.

Bacterial Method of Detecting Lactosuria. Aldo Castellani, J. A. M. A. **90**:1773, 1928.

1. During January and February of this year, I was able to study twelve nursing women whose urine reduced Fehling's solution. In most of the cases the reaction was slight and disappeared after a few days. The bacterial method showed that in every case the Fehling reducing substance was lactose; no dextrose or any other sugar apart from lactose was present.

2. The simplified bacterial method for the detection of lactosuria is easy and may be satisfactorily carried out in any ordinary bacteriologic laboratory.

I shall be pleased to supply workers interested in the subject with the strains of *B. coli* and *B. paratyphosus* B that I use.

Author's Summary.

Flattened Capillary Tubing for Microscopic Examination of Cultures. W. S. Sturges, J. Infect. Dis. **42**:444, 1928.

Glass tubing flattened to form capillaries with lumens from 30 to 40 microns wide and 5 microns thick can be used for culture tubes. Such capillaries lie flat on a microscopic slide to which they can be attached by a drop of cedar oil, and anaerobic cultures sealed within can be watched over a period of days without incurring the danger of exposure to the air.

Occurrence of Lipoids in Urine and Their Diagnostic Importance. E. L. Miloslavich, J. Lab. & Clin. Med. **13**:542, 1928.

The occurrence of doubt refracting (polariscope) fat substances in urine, occurs in the following conditions: (1) lipoid nephrosis of unknown origin (genuine lipoid nephrosis); (2) lipoid nephrosis of syphilitic etiology (secondary stage of syphilis);

(3) subacute and chronic glomerulonephritis (combination forms of nephritis and nephrosis); (4) amyloid nephrosis with edema; (5) Grawitz tumor (so-called hypernephroma) of the kidney, and (6) lipoid carcinoma of the prostate.

S. A. LEVINSON.

A CLINICAL TEST FOR URINARY ACETONE AND DIACETIC ACID. J. A. BEHRE, J. Lab. & Clin. Med. **13**:770, 1928.

The reagents used are salicylic aldehyde and a concentrated solution of sodium hydroxide. The urine is heated in a test tube in a boiling water-bath, and as the vaporized acetone rises, it is brought into contact with the reagents which are suspended over the mouth of the tube on a piece of cotton. Three cubic centimenters of urine are placed in the clean test tube, and 1 drop of 50 per cent concentrated sulphuric acid is added to facilitate the transformation of diacetic acid to acetone. A small, thin square of cotton, of good quality, is prepared, and 1 drop of pure undissolved salicylic aldehyde is dropped on the center of it. Two drops of 32 per cent sodium hydroxide are then applied over the spot of aldehyde. The two reagents solidify on the cotton to form a flat yellow disk. The cotton is then inverted over the mouth of the test tube so that the spot formed by the reagents is turned down toward the urine. The cotton may be pushed down slightly into the tube to keep it in place, but in such a way that the disk formed by the reagents does not touch the sides of the tube. The tube is then placed in a boiling water-bath for eight minutes. In the presence of acetone or diacetic acid, which is changed to acetone, a color varying from pink to deep rose is formed with the reagents on the cotton, quite distinct from the yellowish color given by a blank. The pink given by the acetone deepens for some time after the cotton has been removed from the tube, so that it is best in some doubtful cases to allow the color to deepen in the air for ten or fifteen minutes before making a final decision. Urine containing 1 mg. of acetone per hundred cubic centimeters or the equivalent amount of diacetic acid, shows a distinct positive color after the heating, when 3 cc. of urine are used. Any interfering substances which would be eliminated by distillation are also eliminated by this method.

S. A. LEVINSON.

THE STERILIZATION AND PRESERVATION OF INFECTED SHEEP BLOOD FOR USE IN THE WASSERMANN REACTION. W. FREISE, Centralbl. f. Bakteriol. **104**:373, 1927.

Freise washes the sheep blood obtained from the slaughter house with a 0.1 per cent calcium chloride and 0.85 per cent sodium chloride solution, and then suspends the corpuscles for twenty minutes in this solution which contains formaldehyde 1 : 500. The blood is then preserved in the calcium chloride—sodium chloride solution containing a formaldehyde concentration of 1 : 5,000. Such blood can be used for the Wassermann reaction for at least a week, and if necessary, up to three weeks.

PAUL R. CANNON.

A SIMPLE METHOD FOR DEMONSTRATING SPIROCHAETA PALLIDA. A. GRUMBACH, München. med. Wchnschr. **75**:688, 1928.

A drop of the fluid (serum tissue extract, etc.) is mixed on a glass slide with a buffered formaldehyde solution:

Formaldehyde (40%) ..... 10 cc.
Buffered phosphate solution..... 90 cc.
(88 cc. M/15 Na_2HPO_4 = 9.078 g/1000 + 12.0 cc.
M/15 KH_2PO_4 = 11.876 g/1000)

The fluids mixed on the slide are allowed to stand five minutes, preferably in a moist chamber, and then are spread out in a thin film and dried in the air. The preparations are stained from thirty to sixty seconds with gentian violet or carbol fuchsin.

E. F. HIRSCH.

SEDIMENTATION REACTION OF ERYTHROCYTES. E. KAUFMANN, Ztschr. f. d. ges. exper. Med. **58**:205, 1927.

The original paper should be consulted for a discussion of the principles on which the sedimentation reaction is based, and for the details concerning the proposal of a standard technic.

B. LUCKÉ.

THE SACHS-GEORGI, THE MEINICKE, AND THE WASSERMANN REACTIONS. N. GASIOROWSKI, Ztschr. f. Immunitätforsch. u. exper. Therap. **52**:138, 1927.

The author compared the Wassermann and the Sachs-Georgi reactions in 23,729 serums, and the Wassermann, Sachs-Georgi and Meinicke reactions (third modification) in 3,408 serums. All were equal as to specificity, but differed as to sensitivity. The order of their sensitivity was Sachs-Georgi, Wassermann, Meinicke. The Wassermann reaction was most sensitive in the primary stage of syphilis; the Sachs-Georgi in secondary and latent syphilis. In tertiary syphilis, all three tests were about equally sensitive. In treated patients, the Sachs-Georgi was more sensitive than the Wassermann. The Wassermann reaction disappeared sooner than the Sachs-Georgi. In all three cases, the method of preparation of the antigen is of primary importance.

PAUL R. CANNON.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Monthly Meeting, May 10, 1928

HARRISON MARTLAND, *President, in the Chair*

ECHINOCOCCUS CYST OF THE LIVER. CHARLES G. DARLINGTON.

This specimen of echinococcus cyst of the liver was from a man 38 years of age, a seaman, born in Malta, first admitted to the Beekman Street Hospital shortly before Christmas (a patient of Dr. Ralph Colp, to whom I am indebted for the privilege of presenting this material). He had received a blow in the abdomen, following which he had collapsed. At the hospital, on examination, the presence of a cyst was noted in the epigastrium. The diagnosis of a probable echinococcus cyst was made. In three or four days, the patient was discharged and was advised to come back for operation. At that time, the blood count did not show any eosinophils. He returned the latter part of March. On examination of his abdomen this time, the cyst was noted to be about the size of a grapefruit, while, at the previous examination, it had been the size of an orange. The blood count still did not show any eosinophils. He was operated on, and a large cyst was removed from the under surface of the liver, on the right lobe. He had a stormy time for about five days, at the end of which, in a state of semidelirium, he got out of bed and broke open his wound. About two or three feet of intestines were protruded. He was put back into bed; the intestines wrapped in sterile towels. Shortly afterward he was sent to the operating room, where the intestines were washed with saline and put back, and his abdomen was closed. He made a complete recovery. About a week after his operation, another blood count was made, which showed eosinophils 9 per cent.

The patient had had the cyst for from fifteen to twenty years.

The gross specimen and sections were shown, as well as lantern slides of the gross specimen, and of a section of a wall of the ectocyst; of moist preparations of fluid from the cyst, showing scolices and hooklets; and of sections of a complete small daughter-cyst with wall, scolices and hooklets.

LIPOID NEPHROSIS. JEROME L. KOHN (by invitation).

Genuine cases of lipoid nephrosis are rare. Many pathologists state that there is not any such entity. These kidneys are from a child, aged 7, who was observed by Dr. Schwarz and myself for four years. The patient had recurrent edema, without hypertension; large amounts of albumin in the urine, but not any red blood cells; a normal blood urea; a high blood content of cholesterol and a low content of serum protein. During the time that the patient was under observation, she had five attacks of peritonitis, four due to pneumococcus type 4, and one to a hemolytic streptococcus. Every time the patient had peritonitis the bacteria were recovered from the blood. The patient died last week during an attack of pneumococcal peritonitis.

The kidneys are large and edematous, and show a large amount of doubly refractive fat in the cortex. Microscopically, the many sections examined thus far do not show inflammatory lesions of the glomeruli.

In another case, also that of a child, a post mortem disclosed kidneys similar to those just described. There was much doubly refractive fat. Microscopically, however, the kidneys showed inflammatory changes in the glomeruli, those usually seen in subacute glomerular nephritis. This case was never considered to be a nephrosis, clinically, and of course is not one. The kidneys are shown

merely in comparison. The child in this case was admitted to Mt. Sinai Hospital three years ago with a history of three weeks of hypertension and edema. The urea in the blood was of normal amount. The cholesterol content was moderately increased. The urine contained albumin, casts and red blood cells. The first child did not have any red cells in the urine. The child in the later case was in the hospital for about two months. She then went home in excellent condition, save for the hypertension, which persisted. The blood chemistry was normal, and the urine contained small amounts of albumin. About two weeks ago, the patient returned to the hospital with meningococcus meningitis, from which she died. Between the time of leaving the hospital and the recent re-admission, the patient was apparently well; that is, she played and went to school as other children did. It is hardly fair to pass any judgment based on the blood chemistry at the last admission. There was a moderate hypertension and a moderately high content of urea in the blood and of cholesterol. The urine contained heavy traces of albumin and a few casts.

DISCUSSION

PAUL KIEMPERER: It is true that lipoid nephrosis is extremely rare. I must confess that I did not believe in lipoid nephrosis until I had seen the first case myself. I was shown a number of cases years ago, and I remember one or two of these I could not accept as nephrosis; I would have called them glomerular nephritis. In addition to this case, we had a case in an adult which was clinically typical, and which, after a very exact and prolonged microscopic examination (because, after all, that is the only way in which one can decide whether the case is true nephrosis or glomerular nephritis with a nephritic component), we found that we were actually dealing with a degenerative disease of the kidney, and not a glomerular nephritis. This was a case of a man about 30 years old. It is interesting that this was a case with syphilis, and I only mention it for the reason that Munk emphasizes that syphilis is one of the main causes of lipoid nephrosis. In our children's cases there is no evidence or suspicion of syphilis. It is, of course, necessary to examine many slides before venturing the diagnosis of nephrosis. Whether nephrosis is actually a disease of the kidneys, or a disease of metabolism, cannot be decided from a study of the kidneys alone. Unfortunately, in the last case, we had permission only to remove the kidneys, and so we could not examine the other organs, particularly the glands of internal secretion.

A COMPARATIVE STUDY OF THE QUANTITATIVE METHODS FOR DETERMINING THE PROTEIN CONTENT OF SPINAL FLUID. T. GARCIA, M. KAMNER AND J. A. KILLIAN.

Ling's colorimetric method of testing specimens of spinal fluid gave high values for protein of spinal fluid obtained from epileptics, although the results obtained in qualitative precipitation tests for increased protein were negative. (Osnato, M.; Killian, J. A.; Garcia, T., and Mattice, M.: Biochemical Studies of the Blood and Cerebrospinal Fluid in Epilepsy, *Brain* **59**:581, 1927). These results suggested that production of color in this method might be due, in part, to a nonprotein compound. Phenols were excluded. In a series of 85 cases of epilepsy, the proteins of the spinal fluid were determined by means of the Albe refractometer, by differences in nitrogen, by the Denis and Ayres' method, and by the colorimetric procedure of Ling. The refractometer proved impractical for the determination of protein in pathologic spinal fluids. Pregl's micro-Kjeldahl technic was employed for the estimation of the total nitrogen and the nonprotein nitrogen. The average deviation of the values arrived at by use of Denis and Ayres' method from those based on difference in nitrogen was 7 per cent. Ling's technic gave results from 10 to 40 mg. higher than those obtained with Denis and Ayres' method, and from 4 to 59 mg. higher than those based on difference in nitrogen. Protein-free filtrate of spinal fluid

gave a blue color with Ling's method, indicating that all the color produced in the procedure is not due to protein. These comparative studies suggest that, of all available methods, the one advanced by Denis and Ayres is the best for use in the clinical laboratory.

THE LACTIC ACID AND THE SUGAR CONTENT OF THE SPINAL FLUID IN MENINGITIS. T. GARCIA, J. A. KILLIAN AND A. DE SANCTIS.

In previous communications (Killian, J. A.: Sugar and Lactic Acid of Spinal Fluid in Meningitis, *Proc. Soc. Exper. Biol. & Med.* **23**:255, 1925-1926; Osnato, M., and Killian, J. A.: Significant Chemical Changes in Spinal Fluid in Meningitis, with Special Reference to Lactic Acid Content, *Arch. Neurol. & Psychiat.* **15**:738 [June], 1926) we demonstrated a rise in the lactic acid content of the spinal fluid in meningitis, and presented evidence indicating that the increased lactic acid is a product of cellular activity. Glaser (Lactic Acid Content of Cerebrospinal Fluid, *J. Biol. Chem.* **49**:539, 1926), also, showed a rise in the content of lactic acid in the spinal fluid in meningitis. An intensive study of the amounts of sugar and of lactic acid in specimens of spinal fluid taken daily from 37 patients with different types of meningitis, suggests that changes in the amount of lactic acid in this fluid are better indices of the progress of the infection, and of its arrest under treatment than are variations in the content of spinal fluid sugar. In meningitis, the lactic acid of the spinal fluid exceeds in amount the lactic acid in the blood; consequently it is not dependent on the lactic acid in the blood. However, the sugar in the spinal fluid is less in amount than the sugar in the blood, and it may vary in amount with the sugar in the blood. The amount of lactic acid in the spinal fluid may fluctuate considerably, although the sugar content of the blood remains negative.

Normal spinal fluid maintained in an aseptic state showed no glycolysis, but specimens of spinal fluid containing a large number of leukocytes showed during incubation a decrease in sugar content and a rise in content of lactic acid.

ENDOMETRIOSIS. REPORT OF TWO CASES: (1) IN AN INGUINAL LYMPH GLAND AND IN THE TRANSVERSE COLON WITH MALIGNANT DEGENERATION; (2) IN A LAPAROTOMY SCAR. KIYOSHI HOSOI AND LOUISE H. MEEKER.

That endometrium may be found at some distance from the uterus is generally accepted. The explanations given have not been accepted as final and, for this reason, additional observations are valuable. The two cases reported in this paper add something to knowledge.

CASE 1.—We are indebted to Dr. John F. Erdmann and Dr. Edward A. Bullard for the complete history of this case of endometriosis in an inguinal lymph gland associated with endometriosis of the groin and endometrial carcinoma of the transverse colon.

Miss H. A. B., aged 30, was unmarried and had never been pregnant. Her menstrual history was normal, beginning at 16 years. When 20 years of age, she had been operated on for a right inguinal hernia. The hernia returned in the scar, which was swollen and tender, especially before and during each menstrual period. The supposed hernia was again removed six years after the first operation, and was found to be a cyst filled with bloody fluid. Relief was not obtained from this second operation, and six months later the operative area was again swollen and painful, especially before and during menses with metrorrhagia. At this time, in a laparotomy, Dr. Bullard found a "chocolate cyst" of the left ovary, attached to right broad ligament. In this broad ligament adjacent to the cyst there was also a perfectly normal accessory suprarenal gland, as shown by the microscopic section. A left salpingo-oöphorectomy and a shortening of both round ligaments were performed. It was doubtful whether or not the tarlike cyst was of the endometrial type, as most of the lining was destroyed, except a few tall cylindrical cells and one or two secreting glands.

Nine years after the first operation, the patient was admitted to the New York Post-Graduate Hospital. The patient again complained of swelling and pain in the right groin, especially following each period. At operation, the inguinal tumor mass was found to be connected with the right round ligament. The entire inguinal growth was removed. It measured 42 by 32 by 21 mm., and, in addition, there was one inguinal lymph node, 12 by 6 by 6 mm. The larger specimen showed numerous cystic spaces filled with both old and freshly clotted blood, embedded in a matrix of fibrous tissue. Here and there, small brownish pigmented areas were present. The microscopic examination showed numerous small and large cysts with a lining of endometrium, composed of branching tubules and stroma cells, similar to the miniature uterine cavity of Cullen. Many of these cavities were distended with blood and contained portions of the cast-off stroma with tubules. In sections stained by Perl's method, iron pigment was demonstrated, especially in and around the endometrial islands.

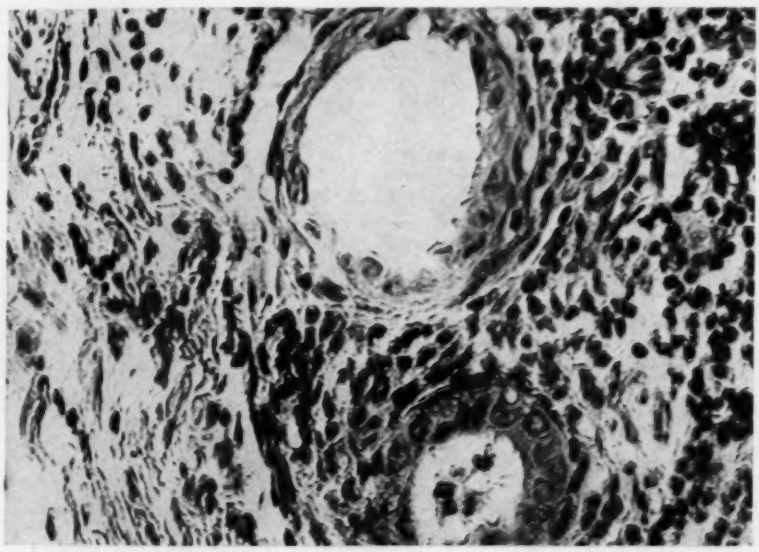

Fig. 1 (case 1).—A medium power photomicrograph of endometrial incisions in an inguinal lymph node. The epithelium is ciliated.

As shown by the van Gieson stain, smooth muscle fibers, also, were present around these glandular areas.

Serial sections of the lymph node revealed five separate, nonbranching, straight gland tubules, ending blindly at both ends. Three of them were located beneath the capsule, the others farther inward. One subcapsular tubule was dilated into a small cyst and was lined by flat or low cuboidal cells, a number of which were ciliated. The lining cells of the other tubules ranged from the tall columnar to the low cuboidal type, with occasional cilia. The lumen was empty or contained granular material and exfoliated epithelial cells. Beneath the epithelium there was a thin layer of spindle cells, which stained yellow by the van Gieson method. Underlying the spindle cells there were endothelial phagocytes, containing blood pigment granules, as proved by Perl's method.

In 1928, the patient was readmitted to the New York Post-Graduate Hospital with symptoms of intestinal obstruction. At operation, 20 cm. of the transverse colon was resected. An unusually severe hemorrhage followed. The obstruction was caused by a tumor mass, 4 by 4.5 cm., with nipple-like projections having

a smooth surface. The lumen was constricted into a narrow slit. The entire thickness of the wall was involved in the neoplastic process. The only ulceration was at the base of the growth. Small firm nodular masses were present on the serous surface, to which tabs of omental fat were adherent. The omental fat contained eight metastatic nodules, with broken down centers, the largest measuring 4 mm. in diameter. At operation, it was seen that the metastases to the liver and mesenteric gland were hemorrhagic in appearance. The cut surface of the main tumor mass was somewhat soft and yellowish gray. In the involved wall of the colon there were numerous cystic spaces; the largest, 14 mm. in diameter, showed numerous papillary growths. The spaces contained mucoid or granular material, which was occasionally deep brown.

Microscopic examination showed an adenocarcinoma, forming the nipple-like projections mentioned. These were covered everywhere by intestinal mucosa, indicating that the neoplasm was invading the mucosa from the deeper

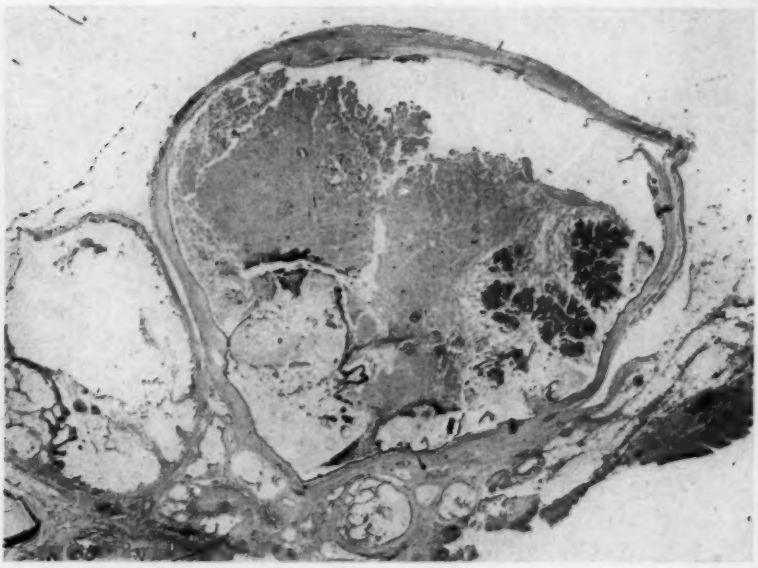

Fig. 2 (case 1).—A low power photomicrograph of an endometrial carcinoma of the transverse colon. The cyst at the left (arrow pointing) is lined by ciliated epithelium.

parts. In the ulcerated area, where the tumor had replaced the intestinal mucosa, there was a sharp differentiation between the tumor cells and the mucosal epithelium. The dilated cystic spaces in the wall of the colon were lined with cells varying in form from flat to tall columnar. The latter were irregular in height, so that the free border of the cells, under higher magnification, formed an irregular surface. In the large cysts were papillary masses of carcinoma. A number of the smaller dilated cysts were surrounded by a thick zone of lymphocytes. Persistent search was rewarded by the finding, on the flat epithelial lining in one of the dilated cysts, of a cluster of definite cilia. Sampson called attention to the fact that cilia were more easily found on the flattened epithelium of dilated gland lumina than on the tall columnar cells. We confirmed this observation.

Comment.—There are three accepted types of tumors of the round ligament: intraperitoneal, extraperitoneal and intracanalicular (in the canal of Nuck). We shall concern ourselves only with the last, which has been interpreted

variously as tumor of the groin, tumor of the vulva and tumor of the lower anterior abdominal wall. In 1903, Emanuel was able to collect from the literature 76 cases of round ligament growths, 15 of which were myomas, fibromyomas or adenomyomas. He added four cases of his own, only one of which was an adenomyoma. Polster, in 1926, found 34 extraperitoneal and 9 intraperitoneal adenomyomas.

As regards pathogenesis, a number of theories have been advanced—Sampson's implantation theory, Halban's theory of lymphatic dissemination, von Recklinghausen's dysontogenetic theory of a misplaced Wolff's or Müller's duct, and the serosal theory of Iwanoff-Meyer. Furthermore, Sampson believes that metastases may occur by way of the veins, as shown by his injection experiments. Each of these theories offers an explanation as to the mode of origin of the different endometrial growths in our case, which is peculiar on more counts than one, as it included epithelial tubules in an inguinal lymph node and adenocarcinoma of the endometrial type of the transverse colon, the latter a new observation.

Epithelial inclusions of the endometrial type in lymph nodes have been rarely observed. In inguinal nodes such inclusions have been found, so far as the literature shows, in but two other cases, those reported by R. Meyer and by Lauche. In the remaining reported cases, the deep pelvic, the iliac and the lumbar nodes were involved. Ries, Wülfing, Sick, Kroemer, Wertheim, Lüthy and Friedlander and Foot believed the inclusions to be derivatives of Wolffer's duct. On the other hand, Meyer, Kermauner and Lameris, Falkner, Brunet, Sitzenfrey, Gutfeld and Schiller believed they arose from the lymphatic endothelium through irritation from chronic inflammation or from the toxic action of associated uterine carcinoma. Halban attributed their presence to dissemination from the uterus through the lymphatics and Sampson added the venous route. All these writers failed to mention the presence of blood pigment, which we found in our case. Lüthy was the only one to report strands of smooth muscle in the delicate connective-tissue trabeculae of the lymph nodes containing the endometrial inclusion. In our case the narrow spindle-cell zone around the inclusion stained yellow, like smooth muscle, by the van Gieson stain. Stroma such as that seen in the normal endometrium in the uterus was not observed in lymph nodes.

Polster, in 1926, collected 80 cases of intestinal endometriosis from the literature. In Sampson's experience, intestinal adenoma of the endometrial type occurred in more than one half of the cases of ectopic endometrial adenomas. He found them most frequently on those portions of the intestinal tract which are usually found in the pelvis. In our case, the tumor occurred in the mid-transverse colon and is perhaps unique in that it occurred above the level of the umbilicus. It is much simpler and pathologically sounder to regard our observations as evidence of one process than to consider them as separate, different entities.

CASE 2.—*Endometriosis in a Laparotomy Scar.*

Miss E. H., aged 40, never pregnant, was admitted to the service of Dr. T. H. Russell (to whom we are indebted for the clinical history). The patient had an appendectomy when 11 years old. Twenty-six and one-half years after the operation a lump appeared in the old appendectomy scar. The lump did not occasion distress until six months before admission to the hospital; at that time it became painful for a period lasting one day. The menses were normal in every respect. The operation revealed a postoperative hernia, in the wall of which there was an ill-defined tumor mass. This mass measured 35 by 20 mm. and looked dense, with gray and red markings. It was incorporated with the under side of the skin and was not demarcated from the surrounding fat.

The microscopic sections showed islands of endometrium-like growth in the tumor mass in the scar tissue. The gland tubules were lined by columnar or low cuboidal cells, many of which were ciliated. Many glands were dilated

and the lining epithelium presented a wavy surface, like the glands seen in the menstrual endometrium. The lumina contained fibrin, numerous red blood cells or other cellular débris. Some of these islands of endometrial tissue were evidently the pseudoglomerular structures of von Recklinghausen. The stroma about these glomeruli was infiltrated with red blood cells, small round cells, plasma cells and occasional polymorphonuclear leukocytes, and it also contained large oval cells like the stroma cells of the uterine mucosa. A reaction of giant cells to a foreign body was present around cotton threads in the immediate vicinity of the endometrial islands. In sections stained by Perl's method, iron pigment, most abundant, was seen in and around the endometrial islands. The van Gieson stain demonstrated that smooth muscle fibers were present.

Comment.—In 1903, R. Meyer reported the first case of endometriosis in a laparotomy scar. To date, 84 cases are on record, including our own. Almost all of these occurred between the ages of 20 and 45 years, with only two cases occurring after 45 years, one at 46 and the other at 50 years. Eight cases were in single women and 23 in married women. There were 28 cases following ventrifixation, 26 after salpingectomy or oöphorectomy, or both, 16 after cesarian section, 13 after appendectomy, 5 after hysterectomy and the remainder after miscellaneous operations on the pelvic organs. The swelling or tumor made its appearance soon after the operation or, as in our case, as late as twenty-six and a half years afterward. The lower end of the operative scar appeared to be the site of predilection. Internal adhesions to the pelvic organs or omentum were noted in 29 cases. The chief symptoms noted were swelling, tenderness and pain, all increased before, during or after the menstrual period. Menses tended to become abnormal with dysmenorrhea or menorrhagia. Ballin's "menstrual fistula," a broken-down blood-filled cyst, occurred in 15 cases. Smooth muscle fibers, lime deposits, blood, iron pigment and suture material have been found, besides the endometrial stroma and gland tubules with cilia.

As regards the pathogenesis of cases found in laparotomy scars, the transplantation theory would seem to explain the majority of the cases, as most occurred after operations on the uterus and adnexa. In Neuweiler's case an endometriosis developed in the scar from a perineal laceration occasioned by a pregnancy five years before. Experimental proof of the possibility of endometrium being transplanted from the uterus to the abdominal organs has been given by Jacobson, Albrecht, Dossena, Michon, Stilling, Ferracciu, Katz and Szenes. Cron and Gey were able to grow human endometrium in tissue cultures. They used the fragments of epithelium (decidua menstrualis) normally found in the menstrual flow and obtained viable cultures. In our case, endometrial tissue from the uterus passing through the tubes or from a possible ectopic endometrioma may have become implanted in the hernial sac. Exploration of the abdominal cavity was not undertaken.

The theory of a serosal metaplasia and the theory of lymphatic dissemination were applied to those instances where a simple appendectomy had been performed and where there was no hernia. Tobler, by serial sections, demonstrated a connection between the ectopic endometrial tissue and the peritoneal serosa, and Dietrich showed the development of glomerular-like structures from the serosa. Ewing believed that one theory could not explain all the cases.

Summary.—In our first case, we described an endometriosis of the groin, endometrial inclusions in an inguinal lymph node and endometrial carcioma of the transverse colon.

Were these implanted from the uterus by the trans-tubal route, or disseminated by veins or lymphatics; or were they from a ruptured ovarian endometrial cyst, or were they embryonal rests or serosal metaplasias? The theory of lymphatic dissemination of Halban offers the best explanation for the tumor of the groin and the inclusions in the lymph node, while the theory of implantation offers the best explanation of the adenocarcinoma of the transverse colon with metastases to the liver and mesenteric lymph nodes.

In our second case, we have described endometriosis developing with a hernia and a reaction to a foreign body in an old appendectomy scar.

Which theory can be applied to this case? Our decision rests between the theory of implantation of Sampson and the theory of serosal metaplasia.

DISCUSSION

GERARD L. MOENCH: The two cases which Dr. Hosoi has presented are interesting from a good many standpoints. Adenomyositis or endometriosis used to be a relatively simple problem as long as all such lesions were supposed to be embryonal. Robert Meyer, however, showed that the wolffian body does not come down below the insertion of the round ligament into the uterus, so that cases below this point must have some other origin and, on the basis of an inflammatory reaction producing changes in the celomic epithelium, he formulated his theory of adenomyositis. It was shown later that these cases of adenomyositis were not necessarily inflammatory, so that Frankl suggested the term adenomyosis. Since then, Sampson's implantation theory has appeared. The clinicians, as a general rule, think highly of this theory, whereas the pathologists are more or less opposed to it. Personally, I have felt, long before I read it in the literature, that endometrial-like structures, even in a laparotomy scar, do not necessarily mean that they are implanted portions of the uterine mucosa. In many cases, I believe they may simply be changed peritoneum, misplaced at operation. Many, I believe, are inclined to forget the changes which the celomic epithelium can undergo. I remember a tube studded with little nodules like tubercles, which were not anything but areas of stratified squamous or transitional epithelium. They show what huge transitions can take place in the celum. Schiller of Vienna has shown experimentally progressive changes in the peritoneal epithelium from the flattened endothelial-like cell to a definitely epithelial cell. This must not strike us as strange when we remember that the germinal epithelium of the ovary is but changed peritoneum, and I have seen cases in which the epithelium of the ovary dipped down and formed tubes and cavities which would easily lead to such structures as Sampson has described. Thus, while I believe that most cases of so-called endometriosis represent celomic changes, I should not entirely discard the embryonal theory. When the allantois and yolk stalk penetrate the abdominal wall to enter the umbilical cord, they carry with them at times a small part of the celum, which may later give rise to adenomyositis. I remember one case, undoubtedly of embryonal origin. The tumor was removed during cesarean section from between the folds of the broad ligament, and it was not connected with the uterus or with the tube. It consisted of typical decidua.

Another point, also, that I think should be remembered is that all cases described as adenomyositis are not really such. I have seen a cyst of the wolffian duct filled with blood of rather tarry consistency and von Franqué has reported a similar case; this simply means that bloody contents do not prove that our lesion is really an endometriosis. Furthermore, so many cases of appendectomy and simple suspensions of the uterus have been followed by adenomyosis of the abdominal scar that the implantation theory of Sampson cannot, in a good many cases, be a proper explanation. The dissemination of endometrium through the lymphatics, as proposed by Halban, has not much proof in its favor thus far and to me seems unnecessary in most cases. In Dr. Hosoi's and Dr. Meeker's case, it does not strike me as particularly strange that the lymph gland showed some involvement, since the tumor was actually carcinomatous. In cases of pseudomyxoma peritonei, pseudomucin is found in the lymph glands. Dr. Hosoi spoke of cultures of endometrium on living tissue. Heim, at the German Gynecological Society meeting in Bonn, in 1927, reported that he never could grow menstrual endometrium unless he actually curetted it off. The cast-off material would never grow. It seems to me, therefore, that endometrium found in a laparotomy scar after cesarean section is more

likely to be a transition of the peritoneum than an implantation of uterine mucosa, since the endometrium after birth is in a degenerating condition.

In conclusion, then, I should say that, to me, at least, the celomic origin of adenomyositis seems an adequate explanation in most cases. Some few cases may be embryonal. But I do not deny that actual transplantation of uterine mucosa may occur at times and thus give rise, in rare instances, to a true endometriosis.

ALFRED PLAUT: I agree with most of the statements of Dr. Moench, but I should like to go a little further. Looking at tubes every day in the laboratory of the Woman's Hospital, I can make the statement that a large number of tubes and broad ligaments show cylindrical cells in the peritoneum. In nearly all cases of long standing hemorrhage in the pelvis, high cuboidal or cylindrical cells are formed in the peritoneum, most of them with the appearance of papillae and of glandlike structures dipping down into the tissues of the tube or other structure lying under the peritoneum. In a large percentage of all cases of chronic inflammation in the pelvis, there may be seen glandlike structures from the peritoneum going down into the tube. I have a slide here which clearly shows the glandlike structures coming from the peritoneum. I have no doubt that they originated from the peritoneal lining cells; they are frequent. If one should make serial sections, the percentage of these observations would become exceedingly high, so that they would be placed among the structures commonly found in the pathologic material from a surgical service. The frequency of these appearances in the peritoneum makes me think that Robert Meyer's serosa theory is capable of explaining the majority of cases of endometriosis. It is not endometrium in the sense of coming from the endometrium. It is tissue which behaves like endometrium, in some respects; but in the most important respect, the cycle, it does not, in most cases, behave like endometrium. Endometriosis (here I agree with Sampson) is a frequent disease; next to myomata uteri it is the most frequent noninflammatory condition in the female pelvis; but it is rare to see the proliferative or secretory phase in ectopic endometrium. Embryonic displacement is seldom needed as an explanation of these structures. When you bear in mind that intestinal epithelium can be found in the kidney or in the fossa navicularis without any other anomaly suggesting displacement, you will have to take into consideration again the earlier notion of a so-called metaplasia. The term adenomyosis is now widely accepted. I was glad to hear that Robert Meyer gave up the idea of an inflammatory origin of the so-called endometriosis. Most surgeons and gynecologists still speak about salpingitis isthmica nodosa as if it were an inflammatory lesion; some think it is associated with tuberculosis or gonorrhea. I see such cases in the Woman's Hospital about once a month, and in the four years I have been there I have seen one or two inflammatory cases. All the others were noninflammatory, and belonged to the large group of adenomyosis. The fact that one succeeds in experiments on animals in transplanting endometrium does not prove that the endometrium-like structures found in the female pelvis have originated in that way. It shows only that they might have originated in that way. When one sees how narrow the lumen of the interstitial portion of the tube is, then it is very hard to believe that endometrial tissue would be thrown out through the tubes so frequently, and the frequency of endometriosis is in striking contrast with the rare reports of endometrial tissue found in sections of the lumen of the tube.

Was this tumor in the intestine a carcinoma? There was a large tumor bulging into the lumen of the intestines, and, I believe, the statement was made that the intestinal epithelium was intact all over the tumor.

KIYOSHI HOSOI: There were metastases to the liver and mesenteric glands.

ALFRED PLAUT: The presence of some structures in the liver and mesenteric glands was mentioned. Were they deep in the liver, or on the surface?

KIYOSHI HOSOI: I was not present at the operation, but Dr. Erdmann said that they were distributed throughout the liver.

ALFRED PLAUT: It is hard for me to conceive that such a large tumor should not have interrupted the mucosa of the intestine at any point. In adenomyosis of the rectovaginal septum I do not know of any case among the 80 or 90 in the literature in which the endometrial tumor really destroyed the mucosa of the intestine. This is of practical importance. In many a case of adenomyosis involving the rectal wall the clinical diagnosis of carcinoma of the rectum is made. When the surgeon makes a resection of the rectum he does so at the chance of killing the patient. When he takes out as much of the mass as he can without damaging the rectum, the patient has a chance of cure. Only a few months ago I was called to the operating room to see a young woman in whom a hard mass was invading the base of the bladder. By chance, I had heard that the patient had complained of dysuria at menstruation and I told the surgeon not to make a resection of the bladder, but to take out what he could, leaving the bladder alone, as I thought it was a rare case of adenomyosis of the bladder. Frozen section showed the typical endometrial glands in the bladder, and the patient recovered. I know that carcinoma from endometriosis is described in the literature, but I have never come across a case; it is important that these tumors in the rectum should not be considered malignant, for extensive operations may thus be avoided.

LOUISE H. MEEKER: In this case, Dr. Erdmann said he had encountered a severe hemorrhage when operating on a tumor of the transverse colon. The patient died four months after the operation. An autopsy was not performed. At the time the tumor of the groin was removed, four years ago, an accessory suprarenal gland was found attached to the broad ligament, and this would seem to favor the embryonal theory.

M. R. ROBINSON: The histogenesis of endometriosis or adenomyoma uteri, and that of salpingitis nodosa or adenomyosalpingitis is today fairly settled. The exhaustive studies of Cullen have shown that it starts from an extension of the uterine lining into the uterine wall, and proceeds from the continued proliferation of the lining cells therein. In my contribution to the "Pathogenesis of Adenomyosalpingitis" (*Am. J. Obst. & Gynec.* 1913, vol. 68, no. 4), I was able to adduce sufficient evidence that this lesion is the result of an extrusion of the tubal mucosa into the tube wall and its further growth therein. Whether or not a preceding inflammation is the etiologic factor is still a question.

Our greatest difficulty, however, is with the histogenesis of heterotopic endometrial proliferations. The topographical occurrence of these growths is so diverse and multiform that it is impossible to claim for them any direct anatomic continuity with the uterine mucosa. For this very reason many theories have been formulated. I have given an analysis of all the prevailing theories in my article (A Critique on the Histogenesis of Heterotopic Endometrial Proliferations, *Surg. Gynec. Obst.* **41**:36 [July] 1925), and have shown that the celomic theory of Lauche, or the serosal theory of Robert Meyer, are the only ones that could be applied to all endometrium-like tumors irrespective of their site and location. What are the basic biologic and anatomic principles of this theory? We know that the undifferentiated celomic epithelium possesses "genetic potentialties" which unfold themselves as soon as differentiation sets in; which, in turn, is due to the unfolding of the proper "genetic forces." We also know that out of the celomic epithelium is formed the uterine and the tubal mucosa, the covering of the abdominal viscera, and the lining of the peritoneal cavity. It therefore stands to reason that under abnormal conditions it would be possible for derivatives of celomic epithelium to manifest a revival of "genetic potentialities." This is what actually takes place in the development of adenomyomatous or endometrial neoplasms. An adenomyoma in an abdominal scar, in the ventrifixation scar; in the wall of the intestine or of the appendix, in the inguinal canal, in the umbilicus, or, in fact, in any place where serosal epithelium is one of the anatomic constituents, an anlage for the formation of the endometrial tumor is present. And not only is this claim substantiated structurally by embryologic facts, but it is also verified functionally by biologic data.

This peculiar tumor formation occurs exclusively in women, during the period of maximal procreative function, and it is influenced by the internal secretions of the ovary. Many clinicians have observed that preceding the onset of menstruation these tumors enlarge and become painful, and that they diminish in size with the onset of the flow. They have thus far not been observed before puberty or after the menopause.

These facts have an important bearing on the etiology of these tumors. Dire results have attended the attempts to remove them when they involved the rectal wall or other parts of the intestinal tract. The splendid results obtained in the treatment of adenomyoma of the uterus with x-rays can be applied to the heterotopic endometrial proliferations with equal success. In my experience the results have been most gratifying.

KIYOSHI HOSOI: I should like to say that numerous sections of the growth showed a typical adenocarcinoma with marked anaplastic characters and numerous mitotic figures, with metastases to the liver. Dr. Sampson, in discussing the various carcinomas of the ovary, showed that the transition from endometrial tissue, endometrioma, into carcinomatous masses is similar to the transition of hyperplastic intestinal mucosa into adenocarcinoma of the intestine.

PHEOCHROMOCYTOMA OF THE SUPRARENAL MEDULLA. C. B. RABIN.

A case of pheochromocytoma of the medulla of the right suprarenal capsule is reported in a woman, aged 45, associated with hypertension. The symptoms were mistaken for those of exophthalmic goiter. The patient died in collapse, showing signs of meningitis. At autopsy, the brain failed to disclose anything abnormal; the heart was hypertrophied and showed epicardial hemorrhages. There was generalized arteriosclerosis and arteriolosclerosis. Examination of the tumor showed a typical pheochromocytoma, within which there were many hyaline droplets. These stained blue with Mallory's aniline blue and remained unstained with phosphotungstic acid and hematoxylin, differentiating them from the hyaline droplets of degeneration in the kidney. I considered these colloid droplets to be an intermediary phase of the secretion of epinephrine. Quantitative analysis of the tumor extract for epinephrine showed 1.5 mg. per gram of tumor. The tumor weighed 40 Gm. It was concluded that the tumor is actively secretory, and that, although a review of the thirty cases reported in the literature suggests that the hypertension and vasomotor instability so often associated with the tumor are directly caused by it, the only way by which this relationship could be shown would be by determination of an increased amount of epinephrine in the blood.

DISCUSSION

M. A. GOLDZIEHER: This case is interesting not only because of its rarity and peculiar morphologic features, but particularly because of its clinical aspects. Dr. Rabin's conclusion was that we cannot claim with any certainty that the epinephrine demonstrated in the tumor was directly responsible for the clinical symptoms. This is an argument which is brought rather generally against those claims that hyperfunction of the suprarenal capsules has anything to do with high blood pressure and with those diseases which are supposed to develop on the basis of chronic hypertension; the main argument is that the excess of epinephrine cannot be demonstrated in the blood. I think this argument is not altogether weighty. It is known that epinephrine is an unstable substance. It is very readily oxidized. Furthermore, the dilution of epinephrine in the blood stream and in the fluids of the body is so great that it does not take much destruction of it to put the remainder beyond detection by the methods commonly used. Nevertheless, I think we overlook important facts if we accept the statements of some physiologists that epinephrine cannot have any effect on the circulation; for its effect depends on many other factors hard to copy in physiologic experiments. The paradoxic response to stimulation with epinephrine is well known. Epinephrine has an effect of hypertension, but it may also cause hypotension. The character of the

reaction of epinephrine depends on many things—on the concentration of the hydrogen ion, and of the various electrolytes in the medium, and on the relation of the cholesterols and phosphatides. Furthermore, the state of the organs and the cells which are supposed to respond to it also determines the effect. Many substances — e.g., the hormone of the thyroid — may sensitize the tissues so that they respond to only moderate stimulation by epinephrine. I cannot see the reasons why we should accept the contention of some physiologists that epinephrine, unless demonstrated in the circulating blood, can have no effect on the blood changes and on the blood pressure. It has been demonstrated in a number of pathologic observations that tumors of the pheochrome tissue are frequently concomitant with hypertension, such as arteriosclerosis; and lesions of the kidney, such as occur in the course of hypertension, show clearly that the suprarenal medulla and the epinephrine have something to do with the development of these pathologic pictures. That is for the clinical side of the problem.

As to the morphology of these tumors, Dr. Rabin has brought up the most important points. The presence of cells of tumor tissue in the blood vessels does not prove the growth malignant. I accept his statement with the remark that not all the cells of the suprarenal medulla and the suprarenal cortex found in blood vessels are there as the result of artefacts. They occur in the blood circulation without artefacts, and it is easy to understand how they occur if one bears in mind how thin the vessel walls are, how easily they rupture, and that a group of cells can be pressed into the circulation easily, as has been seen in other organs. In eclampsia and other conditions in which sudden changes in the blood pressure occur, the presence of parenchyma cells in the capillaries of the liver and the lung is common. One has to bear in mind that considerable alteration in blood pressure is physiologic in the suprarenal capsules, as the circulation there is regulated by a peculiar musculature of the suprarenal veins. Muscle bundles are distributed liberally around the veins, particularly where the small cortical veins empty into the larger sinuses. It seems that the configuration of the musculature is such that its contraction inhibits the flow of cortical fluid into the center of the organ, or prevents the discharge of medullary secretion into the central veins of the suprarenal gland. In other words, this peculiar musculature gives us the morphologic impression that its task is to regulate the suprarenal discharge into the blood of the organ and secure a proper mixture. In recent investigations I have shown that this musculature is different in normal individuals from that in patients with hypertension. In persons with hypertension, the size of the muscle bundles averaged about four to one in the normal person. I have found a similar hypertrophy in only a few cases without hypertension, and in these it could be explained on another basis. I think that muscular hypertrophy of the suprarenal veins in hypertension is another argument in favor of the conception that the suprarenal gland is perhaps the main organ responsible for alterations in blood pressure.

C. B. Rabin: Perhaps I did not wish to emphasize the necessity of the determination of an increase of epinephrine in the blood, since this is not feasible with present methods, in order to draw the conclusion that the hypertension described in various cases in the literature is due to absorption of epinephrine and to the effect of that absorbed epinephrine on the blood vessels. I should infer that this is so, on clinical grounds, but nevertheless I think one must be conservative; for drawing this conclusion in this particular case would mean that we should have to draw a similar conclusion as to the action of epinephrine in all conditions of hypertension. The evidence for its being the cause here is circumstantial. That it is the cause is an impression one gains from these cases, but the only proof lies, I believe, in the determination of increased epinephrine in the blood.

Kidney-Suprarenal Interrelationship. David Marine.

Certain observations suggest that the suprarenal gland exerts an influence on the function of the kidney.

First: Cow observed that output of urine was less when a cat's kidney was perfused through the aorta than when perfused through the renal artery. This

led him to suspect, and later to demonstrate, a direct venous connection between the suprarenal medulla and the kidney.

Second: Pathologists have long recognized the frequent association of enlargement of the suprarenal gland with chronic nephritis. This enlargement involves mainly the cortex, although some have claimed that it involves the medulla and is associated with an increased storing of epinephrine. The attempt of the French school to associate the hypertension of nephritis with increased output of epinephrine has not been established. The extensive pharmacologic and physiologic literature on the influence of epinephrine on renal function indicates that, in minimal effective doses, epinephrine contracts the kidney and reduces the output of urine.

Third: In contrast with the enlargement of the suprarenal gland associated with nephritis, the Mackays demonstrated that nephrectomy in rats (surviving from 75 to 90 hours) caused a distinct hypertrophy of the suprarenal cortex.

Fourth: Marshall and Davis (1916) first emphasized the retention of nitrogen in suprarenalectomized cats. This retention began as early as the second day and while the animal's general condition was good. Their observations have now been abundantly confirmed on dogs, rabbits, and cats. The effect of administration of water in prolonging the life of suprarenalectomized animals may be due to diuresis.

Fifth: The kidneys of suprarenalectomized cats, rabbits and rats were studied morphologically. All showed changes, differing mainly in degree, and were similar to those reported by Hartman. The cat showed the most striking changes, probably because the cat's kidney is normally rich in lipoids. In the cat, the kidney began to enlarge as early as the second day, and the changes developed rapidly. The cortex was increased in thickness and became bright yellow; it was softer than normal and felt fatty. Microscopically, the appearance was that of an acute tubular nephritis or nephrosis. The glomeruli were apparently normal, while the epithelium of Bowman's capsule and the convoluted tubules became markedly swollen. The stain sudan III showed that the swelling was due to a marked increase in substances which absorb this dye. At first, the fatty material was finely granular; later the granules became agglutinated into larger masses, and finally extensive degeneration of the epithelium occurred, with formation of fatty casts. Coincident with the increase in the material staining with sudan III, there was an enormous increase in isotropic lipoid. In rabbit and rat, the kidney showed changes similar to those in the cat, but of less degree. Increase in the substance staining with sudan III, was not observable in other organs, suggesting that this lesion was confined to the kidney. Operations other than those causing suprarenal injury did not produce it. What, if any, bearing these renal changes have on the problem of nephrosis offers at present interesting speculation.

DISCUSSION

PAUL KLEMPERER: There is a close resemblance between these experimental renal lesions and the lesions of lipoid nephrosis, shown tonight. There is, however, one point I should like to bring out sharply and that is: In lipoid nephrosis one has to consider two morphologic factors, the fat in the tubular epithelium as well as vacuolar degeneration of the epithelium, which is always present. I should like to ask Dr. Marine whether the fat in his cases was doubly refractile. The mere presence of sudan III granules does not imply that one is dealing with lipoid. One finds such within the tubular epithelium not only in this condition, but also in acute yellow atrophy and in phophorus poisoning and in other conditions; but here the fat is not doubly refractile but isotropic. For the diagnosis of lipoid nephrosis the fat must be isotropic. The second point requires a question: Did you regard the presence of fat in these animals as an evidence of infiltration or of degeneration. I am using the old term because I think, for the kidney, it is permissible to speak of fatty degeneration. In lipoid nephrosis, the presence of fat is infiltrative. However, there is also present a component inducing severe degeneration, and one can demonstrate that whenever there is an amount of lipoid present there is also at hand a severe vacuolar degeneration of the epithelium of the convoluted tubules. In our case, it was peculiar that the degeneration was mainly present in the first portion

of the convoluted tubules. It has been stated in the literature that the severe degeneration is present mostly in the terminal portions of the convoluted tubules. I do not know whether or not our case constitutes a variation. It is true that we were dealing with a meningococcal infection, which might account for the severe degeneration. However, in all the cases there was another cause of death besides the lipoid nephrosis, namely, a superimposed infection — for example, pneumococcal or streptococcal infection. This might account for the presence of severe vacuolar degeneration. Therefore it need not be present in Dr. Marine's experiments, in which the animals were killed.

Another point in differentiating between lipoid nephrosis and these lesions in animals is: If you attempt to make a diagnosis of lipoid nephrosis you do not base your diagnosis on renal evidence alone, but on other discoveries too; namely, of the presence of edema and albuminuria. I do not know whether in these animals there was edema or albuminuria.

It is important that attention be attracted to the examination of the suprarenals in cases of lipoid nephrosis, and also in cases of nephritis in which there is a component of marked nephrosis present. It may be that lipoid nephrosis does not have anything to do with the kidney at all. I should favor the idea. Certainly, however, in the nephritides with a component of lipoid nephrosis, one must assume that the kidney is diseased, and decide whether or not the component of lipoid nephrosis is independent of the renal disease. I do not venture to say this without having started to examine the suprarenals in such cases, since Dr. B. S. Oppenheimer has called my attention to the possible relationship between nephrosis and the suprarenals, and suggested a close examination of the suprarenal in this and another case. So far, I must say I cannot detect anything pathologic. That may not mean anything, but I should like to know what one should expect in the suprarenals in such cases. In Dr. Marine's animals the suprarenals were completely removed. Therefore, in human beings, you would expect at least a severe lesion. Grossly, however, the suprarenals did not show any conspicuous evidence of disease in these two cases. Microscopically, I did not see anything unusual.

MAX GOLDZIEHER: I want to make two points about the possible relationship of the suprarenal function to the kidneys. Experiments that I made in 1908 taught me that if you inject an emulsion of kidney substance into rabbits you get a hyperplasia of the suprarenals, and a demonstrable epinephrinemia. These changes are sometimes concomitant with lesions of the arterial wall. I became further convinced that there is an intimate relationship between the suprarenal gland and the kidney on examination of the epinephrine content of the glands in normal and in nephritic persons. The epinephrine content of the glands was determined in a large number of cases, and the average content in cases of nephritis was found to be 50 per cent more than that in the normal person. Sometimes the epinephrine content was 100 per cent above the normal average. There is also the question of the effect that removal of the suprarenals has on the kidneys. In investigations which I have been carrying on in the last two years, I have succeeded in isolating an active principle from the suprarenal cortex. The results will be published soon. This substance, when injected into animals, produces a rapid fall in the lipoid content of the blood. The fall reaches its lowest point in from one half to one hour. After a single injection, the lipoidal content of the blood returns to the normal level within four hours. It seems, therefore, that the hormone of the suprarenal cortex has a definite effect on the content of lipoids in the blood, and regulates their distribution. I have tried to find out what happens to the disappearing lipoids. I have injected animals with cholesterol intraperitoneally to get a higher content of cholesterol in the blood. After injection of the cortical hormone there is an enormous infiltration of the reticulo-endothelial cells with cholesterol, while such infiltration is absent in the control animals. It seems that the cholesterol and other lipoids, when taken out of the blood, are fixed in the tissues, particularly in the reticulo-endothelial cells. It seems to me that if the suprarenal cortex is removed, and the suprarenal hormone is lacking, one is going to get a higher content of lipoids in the blood and the same clinical pictures, practically, as one gets in nephrosis. Therefore, it is easy

to understand why one gets an infiltration of the parenchyma of the kidney with these lipoids. I wonder if an examination of the kidneys has shown that we are dealing with both types of fat.

To answer Dr. Klemperer's remark — I think I am of his opinion that the degenerative changes of the parenchyma of the kidney have not anything to do directly with nephrosis, and I venture this opinion on the basis that persons with nephrosis have been known to live for many years. I cannot conceive of anyone with a degenerative disease of the kidney lasting for so long a time. Such lesions would not be compatible with life. Therefore I think the degenerative changes in the parenchyma are due to a condition which accompanies the nephrosis and which does not have anything to do with the nephrosis proper, but is due to an infection with *Meningococcus, Pneumococcus* or some other infectious agent.

DAVID MARINE: As regards the presence of antisotropic lipoids, they are markedly increased in these kidneys. I prefer to call the change fatty metamorphosis. It is certainly, in the beginning, a marked infiltration and swelling of the tubular epithelium; degenerative changes may occur very late.

Like nephrosis, this lesion also begins in the proximal convoluted tubules, then extends into the distal tubules and finally involves the loops. Morphologically, therefore, the two conditions have many features in common, but there are a great many differences, also, between this lesion and the disease of lipoid nephrosis. Human beings with nephrosis show a lowered content of calcium in the blood; these animals have a high content of calcium in the blood. Nephrosis could not be due entirely to the suprarenal gland, since the latter may be seriously injured, as in Addison's disease, and not develop that lesion.

As regards Dr. Goldzieher's point, whether or not this kidney lesion is caused by the lack of some cortical hormone — I am not in a position to say whether it is a medullar or a cortical effect. If it should be found that the precursor of epinephrine is produced in the cortex, then immediately all the experiments so far done to show that the two portions have different functions would lose validity.

EXHIBIT: TYPES OF TRAUMATIC CEREBRAL HEMORRHAGES. HEMORRHAGES DUE TO CONCUSSION AND THEIR RELATIONSHIP TO POST-TRAUMATIC PSYCHOSES, AND TO THE CONDITION KNOWN AS "PUNCH DRUNK." HARRISON S. MARTLAND.

A series of photographs, charts, slides and other material was shown demonstrating various types of traumatic cerebral hemorrhages encountered at autopsy.

Analysis was made of 309 consecutive autopsies of people dying as the result of cerebral injuries in a community of about 800,000 population, the exhibit and analyses representing practically all the deaths due to cranial injury (exclusive of cranial injury due to gunshot wounds) during a two-year period. The number is sufficiently large to allow of a conclusion as to the incidence of the various types of traumatic intracranial hemorrhages.

Extradural hemorrhage was found in 25 cases, or in 8.2 per cent; cortical laceration and hemorrhage, in 254 cases, or in 82 per cent; and deep multiple punctate hemorrhages without fracture of the skull or gross surface injuries in 9 cases, or in 2.9 per cent. Unclassified subdural and pia-arachnoid hemorrhages and multiple, streaky, deep hemorrhages associated with cortical injuries were present in 21 cases, or in 6.9 per cent.

The extradural hemorrhage was always associated with a fracture of the skull, usually of the vault, extending downward into the middle fossa along its least convex surface, and tearing either the anterior or the posterior branch of the middle meningeal atery, or the main artery itself near the foramen spinosum. The anterior meningeal artery was ruptured in only one instance. Its clinical picture is usually clear cut, the lucid interval fairly characteristic and the treatment in uncomplicated cases is well known.

Cortical laceration and hemorrhage characterized by laceration of the vessels of the leptomeninges with hemorrhage in the pia-arachnoid and the cortex of the brain constituted by far the most frequent and most important traumatic lesion

within the cranial cavity. This type of injury occurred in 254 cases, or in 82 per cent. In 47 cases, the brain was injured directly beneath the point of violence; in 177 cases, the hemorrhage was due to contrecoup, and in 30 cases it had resulted from a combination of direct injury and contrecoup. The usual postmortem observation was hemorrhage in the pia-arachnoid, either directly beneath the point of violence, or at the site of contrecoup or in both places, associated generally with small, multiple hemorrhages, occasionally punctate, but commonly streaky, in the gray cortex, running at right angles to the surface of the brain. In the majority of cases the underlying white matter was fairly free. Where the injury was extensive, confluent areas of softening extended into the underlying white matter.

The object of this exhibit was to call attention to the nine cases in which multiple, punctate hemorrhages were found in the deep parenchyma of the brain, which were unassociated with fracture of the skull or any serious injury to the leptomeninges or the cortex of the brain. While this type of brain injury has been recognized by men performing medicolegal autopsies, it has never attracted sufficient clinical attention. In 1924, Cassasa reported before this society five autopsies showing this type of hemorrhage. He spoke of them as concussion hemorrhages and attributed their formation to the sudden overfilling of the perivascular lymph spaces by cerebrospinal fluid forced back from the cortical pia-arachnoid spaces by the direct effect of the violence on the overlying skull. The mechanical distention of the spaces of Virchow-Robin often ruptured the network of fine fibroglia connecting the external walls of the blood vessels to the surrounding brain tissues across the perivascular spaces, and a consequent laceration or tearing of the wall of the vessel produced a hemorrhagic extravasation into the perivascular space. It is conceivable that the milder cases of concussion may be attributed to distention of the perineuronal spaces in a similar manner causing hydraulic shock to the neurons without the occurrence of actual hemorrhages.

In 1927, Osnato and Giliberti studied 100 clinical cases of concussion of the brain with or without fracture of the skull and one of Cassasa's cases from the pathologic standpoint. They concluded that "anatomical and clinical investigations seem to show definitely that our conception of concussion of the brain must be modified. It is not longer possible to say 'that concussion is an essentially transient state which does not comprise any evidence of structural cerebral injury.' Not only is there actual cerebral injury in cases of concussion but in a few instances complete resolution does not occur, and there is a strong likelihood that secondary degenerative changes develop. When this happens, we have a condition which, clinically at least, resembles some of the reactions seen in encephalities. We feel, therefore, that the postconcussion neuroses should properly be called cases of traumatic encephalities."

When the skull was fractured, this type of hemorrhage did not occur, since the splitting of the skull at the time of the violence seemed to prevent the increased intracranial pressure.

The possibility of fat embolism causing these hemorrhages was first recognized by Cornwall, who had examined one of Cassasa's cases and found evidence of fat emboli in the brain. Fat embolism presents the only serious argument against the mechanical theory of Cassasa. Fat embolism can be demonstrated at autopsy after nearly all fractures of the long bones, and also has been seen after operations on obese subjects, especially such as radical amputation of the breast and herniotomy for umbilical hernia. Bissell thought it might explain certain deaths following these operations, formerly attributed to surgical shock. The increased viscosity of the venous blood causes a rise in venous pressure and a fall in arterial pressure similar to that seen in shock.

It is the consensus of opinion, however, that fat embolism rarely causes serious symptoms or results fatally. Most of the fat reaches the lungs and is held there. At autopsy, oil droplets may be seen with the naked eye in the blood from the right side of the heart, large veins and lungs, provided the proper technic is used in the autopsy. In some cases, a considerable amount may reach the systemic circulation

and cause petechiae in the skin and pleura and microscopic evidence of fat in the brain, spleen, kidneys, etc. Systemic emboli are more likely to occur if the foramen ovale is patent and in such cases multiple, punctate hemorrhages have been seen throughout the white matter of the brain in enormous numbers after a simple fracture of the femur. In six of the nine cases reported by Beling and Martland in 1927, the injuries were limited entirely to the head, and fat emboli were eliminated as far as possible. The mechanical theory of Cassasa best explains most of these hemorrhages, but fat embolism might occasionally produce similar lesions. The ringlike distribution of these hemorrhages about the vessels is not characteristic of trauma alone. A similar location of the hemorrhages is seen in fat embolism, arsenical encephalitis, hemorrhagic forms of influenza encephalitis, etc. In encephalopathia postgripposa (epidemic encephalitis) the ringlike perivascular collections of the inflammatory defense cells are similar.

The clinical importance of this type of traumatic cerebral hemorrhage has never been fully appreciated. I believe that such hemorrhages form the foundation for a replacement gliosis, which explains the occurrence of posttraumatic symptoms in many cases of head injury. It forms the best anatomic explanation of the large and important groups of postconcussion neuroses and psychoses, the so-called posttraumatic encephalitis, etc. Its medicolegal importance, especially to labor compensation boards, etc., becomes at once apparent.

For some time fight "fans" and fight promoters have recognized a peculiar condition occurring among prizefighters which they have termed "punch drunk." Occasionally they speak of the condition as "the boxers' waltz," "cuckoo," "cutting paper dolls," etc.

"Punch drunk" occurs most often in fighters of the slugging type, who are poor boxers and who therefore take considerable head punishment, seeking only to land a knockout blow. It is common, too, in second rate fighters used for training purposes, who are sometimes knocked down several times a day. Frequently it has taken from one to two hours for a fighter to recover from a severe blow on the head. In some cases, consciousness is lost for a considerable period of time.

The early symptoms of this condition are a slowing down in muscular action, sometimes a peculiar mental attitude characterized by hesitancy in speech, a sudden flopping of one foot or leg or even a dragging of the whole leg. Tremors of the hands and nodding movements of the head may occur. This condition is so well known to fight "fans" that they often shout at the fighter in the ring "Cuckoo." Many cases remain mild in nature.

In severe cases there may be a peculiar tilting of the head, a marked dragging of one or both legs, a staggering, propulsive gait with the facial characteristics of the parkinsonian syndrome, or a backward swaying of the body, tremors, vertigo, deafness, etc. Finally marked mental deterioration may set in necessitating commitment to an asylum.

Of course, the symptoms of syphilis, encephalitis and other diseases may resemble the condition described and must therefore be ruled out. The fact that the symptoms have been well recognized in fighters and the fact that 50 per cent of them, if they have kept at the game long enough, develop the symptoms, is evidence that a lesion due specifically to their occupation exists.

As far as I know, this condition has not been described in medical literature.

I am of the opinion that in "punch drunk" there is a definite injury of the brain due to repeated blows on the head, in the nature of multiple concusion hemorrhages, which later produce a replacement gliosis. The regions affected are chiefly in the basal ganglia. Hence the symptoms may mimic those seen in diseases characterized by the parkinsonian syndrome. The histories of twenty-three prizefighters, including some "topnotchers," who are known by a competent authority to suffer from the condition termed "punch drunk," were exhibited.

I have examined some of these men and have demonstrated clinically that their present condition is not due to syphilis or the sequela of epidemic encephalitis. At this time five are in insane asylums.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, May 10, 1928

J. HAROLD AUSTIN, M.D., *Presiding*

BOECK'S SARCOID LESIONS INVOLVING THE VISCERA. MITCHELL BERNSTEIN, FRANK W. KONZELMANN and D. M. SIDLICK.

S. M., a man, aged 52, was seen on July 3, 1926, by one of us (M. B.), complaining of weakness and the presence of pigmented areas in the eyelids and ears and on the face and trunk. These pigmented areas had been present for two months prior to the patient's first visit. The family history was not of any importance.

In May, 1926, the patient first noticed the presence of the nodules in the ears, then in the eyelids; later they appeared on the face, arms and trunk. The outstanding features observed when first examined were: cutaneous lesions which consisted of reddish, telangiectatic, violaceous nodules; they were irregular in outline, did not itch and varied in size from that of a pea to that of a walnut. These nodules did not show any tendency to ulceration or to heal.

The patient's Wassermann reaction was 3 plus.

On Aug. 18, 1926, the patient had become much weaker. He had developed a productive cough and had had several attacks of hemoptysis. The cutaneous lesions remained unchanged. The physical examination at this time revealed the presence of a bilateral hydrothorax which extended to the fifth rib, posteriorly on the right side and up to the sixth rib posteriorly on the left side.

X-ray examination of the chest confirmed the presence of a bilateral hydrothorax. The report also stated that x-ray evidence of pulmonary tuberculosis was not present. The x-ray studies of the gastro-intestinal tract were negative.

Repeated examination of the sputum failed to reveal any tubercle bacilli, spirilla or fungi. The blood chemistry on August 18 was: nonprotein nitrogen 40, urea nitrogen 22, uric acid 6.2, creatinine 1 and blood sugar 101.

The pleural fluid was dark and at times bloody. The specific gravity ranged from 1.010 to 1.016; there was odor, and the fluid was sterile on culture. The cell count was 795 per cubic millimeter. The differential count was: polymorphonuclears 13 per cent, lymphocytes 71 per cent, endothelials 6 per cent, mononuclears 4 per cent and eosinophils 6 per cent. The fluid injected into the peritoneal cavity of a rabbit proved negative for tuberculosis. The Wassermann reaction of the pleural fluid was 4 plus.

The patient grew progressively weaker and died of bronchopneumonia on Nov. 27, 1926. During the last eight weeks of the patient's life, he suffered with severe, unexplainable abdominal pain and marked constipation.

The case is of interest clinically. It calls attention to the fact that the pleural effusion, the abdominal pain, constipation and other symptoms complained of by the patient may well have been caused by the sarcoid lesions involving the vital organs.

DISCUSSION

DR. SIDLICK: First under the name of multiple benign sarcoid and later under the name of multiple lupoid, Boeck was the first to describe a cutaneous disease which manifested itself by the presence on the skin of small nodules, large nodules or infiltrated patches having a characteristic microscopic picture.

The varying forms of this disease may begin suddenly with a diffuse edematous reddening, and after several days may disappear and leave infiltrated areas. More often it begins as a round nodule, deep in the cutis, and as it approaches the cutis, lifts it up. The nodules grow slowly, come out in crops and remain months or even years. The lesions may vary in number from one to many hundreds. They usually appear on the face, spreading to other parts of the body, gradually involving the extremities and trunk. These efflorescences at the beginning are rose red, but later assume a bluish red tint in the centers, and a yellowish brown dis-

coloration at the periphery. On close inspection, a network of delicate capillaries can be seen in the central areas. The nodules feel hard and often, on pressure with glass, show minute yellow foci. This led to the name of miliary lupoid.

Boeck considered the disease as infectious granuloma. Occasionally, it was possible to recover tubercle bacilli from experimental animals, but on the whole, evidence is lacking that tuberculosis is the cause. The positive Wassermann reaction in this patient, I believe, is a coincidence. It does not have any bearing on Boeck's sarcoid.

Since the postmortem examination revealed the involvement of vital organs and tissues, the presence of Boeck's lesions should prove of significance and interest to the internist as well as to the dermatologist. From the evidence obtained at necropsies and from a review of the literature on the subject, it is more than an assumption that the lesions first invade the organs and tissues and not until a later date appear on the skin.

DR. KONZELMANN: At the autopsy, the body was emaciated. Dark red nodules were found in the skin of both external ears, both upper eyelids, over both malar bones, on the thorax and on the abdomen. They were irregular, slightly elevated and hard but not ulcerated. Pressure did not cause the disappearance of the color. Similar lesions were found in the epicardium along the course of the coronary vessels, in the mucosa of the bronchus and in the mucosa of the small intestine. When incised, these nodules had the appearance of organizing blood clot. In the intestine, most of them were ulcerated. In all cases they measured from 0.5 to 1 cm. in diameter.

The cellular structure varies in such a manner as to suggest successive stages of development. What seems the early lesion is characterized by an area of marked hemorrhage in which one sees many endothelial lined spaces filled with red blood cells. The area contains also large mononuclear leukocytes, lymphocytes, plasma cells and a few eosinophils. Bundles of spindle cells are found in the periphery, branching and interlacing in a disorderly manner. Capillaries are fewer here, but their lining cells are larger and are more deeply stained. The peripheral spindle cells behave much like fibroblasts and seem to grow toward the center of the nodule. They are accompanied by prominent capillaries and by large mononuclear, oval-shaped cells resembling the endothelial leukocyte of Mallory. Thus a picture is produced in which a nodule is formed of irregular branching and interlacing bundles of spindle cells. Between the bundles, budding capillaries, endothelial leukocytes, a few lymphocytes and plasma cells are found. It is in this stage, which looks like one of attempted repair, that the lesion slightly resembles a neoplasm. A further evidence of healing is the appearance of collagen between the spindle cells. It is found in varying amounts. In some nodules there is little, and in some much of the nodule is made up of collagen in the form of coarse wavy fibrils or a homogeneous substance. In this, the healed stage, a few mononuclear leukocytes and much brown pigment are found with or without recent hemorrhage.

Cultures of the tissues were not made, but sections were stained for bacteria (including the tubercle bacillus) and examined for *Spirochaeta pallida*, but none was found.

The cause of death was bronchopneumonia.

The peculiar tendency to hyaline thickening of the newly-formed capillaries in the lesion and of the arterioles in the vicinity of the lesion was noted with interest. It could not be ascertained whether such sclerosis is a part of the sarcoid process or whether it is due to syphilis, as suggested by the patient's Wassermann reaction.

JUVENILE CIRRHOSIS ASSOCIATED WITH INFECTION. V. H. MOON.

This report centers about two cases of atrophic cirrhosis, one in a boy, aged 14, and one in a girl, aged 12. Both had marked splenic enlargement, a firm, nodular, contracted liver, anemia, loss of weight and a tendency to bleed. Shortly before death, the boy had profuse ascites. Ascites was not present in the other case.

Such cases occurring in children are not rare. Seitz summarized 320 cases in the decade preceding his report. Of these, 31 occurred in breast-fed infants, 72 in young children and 217 in children of school age. There are occasional reports of cirrhosis in two or more children in the same family.

Clinical features include splenic enlargement, hepatic enlargement, gradual onset, slowly developing anemia which frequently is marked in degree and a tendency to bleed from the nose and mouth. Edema, ascites and jaundice are frequent manifestations in the late stages. The similarity of these symptoms to those of Banti's disease makes the clinical differentiation difficult. A satisfactory pathologic differentiation has not been shown.

In cases of juvenile cirrhosis, the liver does not present features differing from those in cirrhosis seen in adults. The course of the disease is more rapid in children, and the changes seen in the organs are less chronic.

The etiology of juvenile cirrhosis is obscure. The same causes are assigned for it as for cirrhosis in adults. Infectious diseases are frequently mentioned as contributing causes. There is lack of experimental or other direct evidence in reported cases that infection has been the cause. The majority of case reports contain the frank admission that the cause is unknown.

CASE 1.—A boy, aged 14, had a past and family history which was without significance, except that one sister had died at the age of 13 years with similar clinical manifestations, resulting in a clinical diagnosis of atrophic cirrhosis. The patient in question ran a rapid course terminating in death ten weeks from the first recognition of abnormal condition. Several weeks subsequent to the patient's death, a younger brother developed a similar condition. His case is still under observation.

When the patient was first seen, the abdomen was distended, and the liver and spleen were greatly enlarged. Examination of the blood showed hemoglobin, 47 per cent; red blood cells, 2,700,000 and white blood cells, 2,600. Ascites and edema were marked features shortly before death.

The spleen weighed 1,120 Gm.; it was smooth and regular in shape. There was no bleeding on section. The pulp was deep red and slightly mottled. The follicles were invisible. The liver weighed 1,330 Gm.; it was uniformly enlarged and pale yellow, and the surface was roughened by innumerable, slightly elevated nodules ranging from 2 mm. to 1 cm. in diameter.

Cultures were inoculated with liver substance. Each of the cultures contained an abundant growth of hemolytic streptococcus. Other organisms did not grow in the cultures. Twelve rabbits were inoculated with this organism. Three of these received subcutaneous inoculations of agar impregnated with the streptococcus, four received intraperitoneal injections of broth cultures and five received intravenous injections of sediment from broth cultures. The rabbits were allowed to live from two to twenty days. In eleven rabbits, the hemolytic streptococcus was recovered from the liver; in three, it was recovered also from the heart's blood, from pericardial fluid once, from pulmonary abscess once, from the spleen twice, from the kidney twice and from the joints once. In three of the four rabbits inoculated intraperitoneally, the peritoneal washings did not contain streptococci at autopsy.

A hemolytic streptococcus, isolated from another source, was inoculated into five rabbits as controls. In only one of the five was this organism recovered from the liver; thus the organism cultivated from the cirrhotic liver showed a greater tendency to infect the liver of experimental animals than did a similar streptococcus from another source.

Sections from the liver and spleen stained by Gram-Weigart's method showed great numbers of cocci growing in pairs or irregularly grouped.

CASE 2.—A girl, aged 12, had manifestations similar to those described in case 1. She bled acutely from the nose and stomach and died twenty-four hours after admission to the hospital. The provisional clinical diagnosis was Banti's disease. The spleen weighed 930 Gm.; it was tough and fibrous. Microscopically, it showed atrophy and fibrosis such as is seen in Banti's disease. The liver weighed

980 Gm.; it was pale, shrunken, irregular, hard and nodular. The gross and microscopic features were those of atrophic cirrhosis.

Sections of both the liver and the spleen stained by Gram-Weigart's method contained cocci occurring for the most part in pairs.

Conclusions.—The presence of infection localized in the liver and spleen was determined in two cases of atrophic cirrhosis occurring in children of school age. Hemolytic streptococci cultivated from the liver of one patient showed a definite tendency to infect the liver in animals. Chronic infection of the liver and spleen should be regarded as a possible cause of cirrhosis. The diagnosis between juvenile cirrhosis and Banti's disease presents difficulties both clinically and pathologically.

PYELO-URETERITIS AND CYSTITIS CYSTICA. EDWARD FENDRICK.

DURAL HERNIATIONS OF THE PIA-ARACHNOID. GERALD H. J. PEARSON.

An unusual condition of the meninges was found in a man dying of progressive bulbar palsy. A number of small slits were found in the dura over the parietal eminences. The pia-arachnoid was thickened, and over the right frontal and both parietal areas there were a number of small white nodules varying in size from that of a pinhead to that of a pea. Under these areas the cortex was atrophied, and the subpial space was distended with cerebrospinal fluid. The arachnoid over the entire brain was thickened and fibrotic, and many arachnoidal cell nests were present. The pia was greatly thickened and fibrotic, particularly over the anterior half of the hemispheres. The nodules consisted of prolongations of the fibrotic upper layers of the pia and were covered by the thickened arachnoid. Cell nests were most numerous in these locations. The nodules of the parietal eminence seemed to underlie the slits in the dura. The most likely explanation of this condition seemed that proposed by Cushing in his discussion of meningiomas. The toxins from the syphilitic infection (evidences of visceral but not of cerebral syphilis were found at necropsy) seemed to have injured the arachnoid, producing fibrosis and cell proliferation. This interfered with the function of the arachnoidal villi, the cerebrospinal fluid pressure rose, and this increased pressure caused further proliferation and fibrosis of the arachnoid and thickening and fibrosis of the pia. As the pressure increased, portions of the pia-arachnoid herniated into the dura. Eventually the fluid pressure became equalized by the central atrophy, but the thickened pia-arachnoid and the herniations remained.

XANTHOMA OF CHOROID PLEXUS. GERALD H. J. PEARSON.

In a man dying of septicemia and miliary abscesses of the brain, the choiroid plexus of the lateral ventricles was found to be enlarged and to be studded with yellow nodules. Except for a single marginal layer of choroid plexus cells, the normal structure had disappeared and was replaced by a number of small tumors separated by fibrous tissue. The tumors were cystic at the center and contained many small linear cavities that probably contained free lipoid material. The cells that composed the tumors were typical xanthoma cells. Many of the vessels showed a perivascular infiltration with small round cells.

Xanthoma of the human choroid plexus is not found frequently, and unless it reaches a size large enough to obstruct the cerebrospinal circulation, it does not produce symptoms. It results from the hypercholesterolemia that follows retention of cholesterol due to injury to the liver. In this case, though estimation of cholesterol was not made, biliary cirrhosis was present.

TWO CASES OF PAGET'S DISEASE (OSTEITIS DEFORMANS) ASSOCIATED WITH MENTAL SYMPTOMS. LAUREN H. SMITH.

Two cases of osteitis deformans in women were presented, both showing definite mental symptoms. The first showed pronounced involvement of the skull, with little advance of the disease in other bones of the body. The onset of the mental illness in this case followed an attack of typhoid fever at the age of 31 and

preceded the first evidence of osteitis deformans by about thirty-five years. The case was typical in that the disease began during advanced life and was insidious in its progress. Although the patient had been resident in the hospital for fifty years, the osteitis was not noticed until about fifteen or twenty years before her death at the age of 81. The psychosis in the beginning, at least, was clearly due to the attack of typhoid. In its later stages, senile atrophy played a part. The patient suffered from mental enfeeblement with occasional episodic behavior reactions. There is not any proof, however, that this had any relation to the gross changes in the skull. Both conditions may have been due to a common cause. The autopsy verified the diagnosis and observations.

The patient in the second case, aged 60, entered the hospital because of an active, confused, disoriented mental state in which she was having hallucinations of sight and hearing, delusions of persecution and periods of excitement. The mental illness cleared up in approximately two or three months, and was characteristic of the type commonly attributed to cerebral arteriosclerosis. It had had a sudden onset similar to a cerebral embolism or hemorrhage, but this followed a year in which irritability, dizziness and emotional instability had been noted. Paget's disease had not been suspected before the patient was admitted to the hospital, and was diagnosed by inspection and verified by the x-ray. Some involvement of the pelvic bones was noted, and there was an ankylosis of one hip, supposedly following a dislocation early in life. Little arteriosclerosis was found (except cerebral arteriosclerosis). There seemed to be more direct association in this case between Paget's disease and the mental illness which the patient in the first case presented.

The cases were presented because the view is usually held that osteitis deformans does not have associated mental symptoms even in late and advanced cases.

Book Reviews

PATHOLOGISCHE ANATOMIE DER TUBERKULOSE. P. HUEBSCHMANN, O. Professor Direktor des Pathologischen Instituts der Medizinischen Akademie in Düsseldorf. Mit 108 zum grossen Teil färbigen Abbildungen. Paper. Price, 86 marks. Pp. 516. Berlin: Julius Springer, 1928.

Huebschmann states clearly in his introduction that he intends to present essentially his own experience and his own conclusions. This work is, then, a monograph and not a textbook; it embodies most of the advantages of the former type of presentation and none of the faults of the latter. It is not unduly burdened with literature, with historic developments and with quotations. The definitely personal and consistent point of view of the author is refreshing and stimulating. Tuberculosis is presented as a pathologic entity the protean manifestations of which gain meaning and significance in the light of a uniform and logical concept. Some of the basic dicta will probably meet with much criticism and some of the morphologic interpretations will be subject to doubt, but every reader will appreciate the scholarly mastery of the subject and its systematic development. In the general part, pathogenesis, histogenesis and the relation of immunobiologic principles to the pathologic changes in tuberculosis are discussed. One of the essential foundations of Huebschmann's system is the work of Ranke. Although he denies allegiance to Ranke's teaching in many important points, the reader recognizes that Ranke's concept of three stages is modified only to three types of manifestations; Huebschmann breaks the chronologic sequence, thus making Ranke's system less rigid and better applicable to facts; but, like Ranke, he describes three clinical and pathologic pictures: the primary complex, generalized forms, and isolated, more or less chronic tuberculosis of one organ system.

The discussion of histogenesis rests on the thesis that tuberculous alterations, like any other inflammatory lesions, are characterized by the lawful sequence of alterative, exudative and productive changes. Caseation is considered always to be caused by the exudative tissue reaction. The necrotic center in a cellular tubercle is, then, not the result of caseation of granulation tissue, but the latter develops secondarily around a caseated, exudative focus. A primarily productive tubercle does not exist. The differentiation into exudative and productive tuberculosis cannot be maintained, since they are only phases of the same process — a revival of Baumgarten's strictest unitarianism. If this opinion — amply supported by histologic studies — is scientifically correct, it does not necessarily apply to the clinical differentiation into predominantly productive and predominantly exudative lesions. The "qualitative diagnosis," critically applied, has produced results so important as to be of greater weight than theoretical deductions from histogenetic observations.

A prominent place is given to studies on miliary tuberculosis, which is the subject of one of the most interesting chapters. The traditional adherence to Weigert's explanation of the pathogenesis of generalized miliary tuberculosis, is severely criticised. Since 1922, Huebschmann and his co-workers have reported weighty evidence to show that the endovascular tubercles — never seen without miliary propagation —— are consequences and not causes of the hematogenous spread. Although the importance of allergic phenomena is stressed, the significance of other factors is duly emphasized, such as the physical nature of the tissue involved, constitutional conditions and the amount and virulence of the infecting organisms.

In the special part — replete with evidential material to substantiate the theories in the first chapters — the manifestations of tuberculosis in the various organs are described with minute accuracy. Here, again, the entire material is taken from the author's own observations. The chapters on pulmonary and lymphoglandular tuberculosis are of particular interest. Pulmonary lesions are represented as propagating and developing exclusively within the respiratory ramifications; this

is claimed to be the case for miliary tubercles, also. Truly interstitial tubercles, in peribronchial or lymphatic tissue, are deemed to be rare and insignificant.

The illustrations are well chosen and unusually well executed. An appendix of about twenty pages contains "remarks on the literature;" these are critical, and at times the discussion of authors more or less disagreeing with Huebschmann becomes somewhat polemic. The index of references is extensive and classified in accordance with the chapters of the book. Its relative incompleteness is fully justified by the general nature of the work; its almost complete national limitation, with an insignificant sprinkling of French references, is open to criticism.

The limitations of this work are characteristic of the strict pathologist. Clinical and roentgenologic studies have contributed significant facts to the pathologic changes in tuberculosis. It does not appear justified to exclude this evidence from consideration because it was not procured by the tools of the pathologist. This criticism applies in particular to the discussion of retrogressive changes. But this is a minor point in comparison to the wealth of information and stimulation that a critical reader will gain from this book which, in the reviewer's opinion, is the most complete and the most modern treatise on the subject.

PATHOLOGISCHE ANATOMIE: EIN LEHRBUCH FÜR STUDIERENDE UND ÄRZTE. Herausgegeben von L. Aschoff Freiburg i.Br. I Band. Allgemeine Ätiologie Allgemeine Pathologische Anatomie. Mit 475 Grossenteils Mehrfärbigen Abbildungen im Text. Seventh edition. Price, 37 marks. Pp. 853. II Band. Spezielle Pathologische Anatomie. Mit 686 Grossenteils Mehrfärbigen Abbildungen im Text. Price, 42 marks. Pp. 1061. Jena, Gustav Fischer, 1928.

The authors of volume 1 and their subjects are as follows: Rössle, internal causes of disease, general pathology of cell and tissue, antibodies and immunity; Askanazy, the external causes of disease; Gruber (in the place of Schwalbe), malformations; von Gierke, disturbances of metabolism; Dietrich, disturbances of circulation; Lubarsch, inflammation; Borst, pathologic growth and tumors.

In volume 2, the distribution of authors and subjects are: Aschoff, heart and pericardium, urinary apparatus, female genital apparatus, digestive organs; Benda, the blood and lymph vessels; Schridde, the blood-forming organs, thymus; Nägeli, the blood; Schmidt, the locomotive organs; Beitzke, the respiratory organs; Ernst, the nervous system; Berblinger, male genital apparatus (formerly by M. Simmonds); Ghon, liver, biliary apparatus, pancreas (formerly by C. Sternberg); von Gierke, glands of internal secretion; Jores, the skin.

In view of the size of the volumes and of the number of illustrations, the price of the work appears to be reasonable. The illustrations are, in general, good; the colored do not always give sufficient details clearly. Each volume has its own index. The presentation is based essentially on German sources. At any rate, the lack of thorough familiarity at first hand with American literature is noticeable. For instance, tularemia, recent discoveries relating to streptococci, and the rôle of copper in hemochromatosis are not discussed. Naturally the various sections are somewhat uneven — an inevitable result with multiple authorship. The chapter on the pathologic anatomy of the skin could be left out without materially reducing the usefulness of the work, which does not include the eye or the ear. But in spite of certain shortcomings, this work continues to be one of the most valuable books in its field.

Books Received

BOLLES LEE'S MICROTOMIST'S VADE-MECUM. Edited by J. Brontë Gatenby and E. V. Cowdry. Ninth edition. Cloth. Price, $7.50. Pp. 656, with 9 illustrations. Philadelphia: P. Blakiston's Son & Company, 1928.

A new, revised and enlarged edition of Lee's well known Vade-Mecum. Since the previous edition in 1921, the death of Arthur Bolles Lee, the original author, has occurred. His place is now taken by J. Brontë Gatenby and E. V. Cowdry, who are assisted by a corps of collaborators. Of the newer chapters of special interest may be mentioned those on the histologic applications of measurements of acidity or alkalinity and of oxidation or reduction, the cultivation of tissues in vitro and its technic, and micromanipulative technic. The work continues to be an unexcelled, up-to-date handbook of the methods of microscopic anatomy in all its details and applications.

ZYTOLOGISCHE UNTERSUCHUNGEN VON ERGÜSSEN DER BRUST- UND BAUCHHÖHLEN MIT BESONDERER BERÜCKSICHTIGUNG DER KARZINOMATÖSEN EXSUDATE. Von Ulrik Quensel. Pp. 183, and 49 plates with 99 figures. Uppsala och Stockholm: Almquist & Wiksell, 1928.

This is a collection of articles that have appeared in *Acta medica Scandinavica*, 1928, vol. 68, and supplement 23, 1928. The main results obtained and the methods of staining used in the work will be referred to in appropriate places in Abstracts from Current Literature.

BIBLIOGRAFIA SOBRE CANCEROLOGIA. Por el Dr. Angel H. Roffo. Traductores colaboradores, Ernesto Schaedler y Yolanda Desrumaux. Tomo 1. Años 1925 y 1926. Paper. Pp. 613. Buenos Aires: "Las Ciencias," 1927.

KONSTITUTIONSSEROLOGIE UND BLUTGRUPPENFORSCHUNG. Von Dr. Ludwig Hirszfeld, stellvertretender Direktor des staatlichen Hygiene-Instituts-Warschau. Paper. Price, 18 marks. Pp. 235, with 12 illustrations. Berlin: Julius Springer, 1928.

DIE BIOLOGIE DER PERSON. Ein Handbuch der allgemeinen und speziellen Konstitutionslehre unter Mitarbeit zahlreicher Fachmänner. Von Prof. Dr. Th. Brugsch und Prof. Dr. F. H. Lewy. Price, 16 marks. Pp. 576. Berlin: Urban & Schwarzenberg, 1928.

LEPROUS CHANGES IN TESTIS, EPIDIDYMIS AND SPERMATIC CORD. W. Kobayashi, Clinical and Etiological Studies of "Safu." T. Matsunaga, Monographiae Actorum Dermatologicorum. A. Series Dermatologica, numbers 2 and 3. Imperial University of Kyoto, Japan, 1928.

ARBEITEN AUS DEM PATHOLOGISCHEN INSTITUT DER UNIVERSITÄT HELSINGFORS (FINLAND). Von Prof. Dr. Axel Wallgren. Pp. 231, with 88 illustrations. Jena: Gustav Fischer, 1927.

COMMUNICATIONS DE L'INSTITUT SÉROTHÉRAPIQUE DE L'ÉTAT DANOIS. Vol. XVIII. Pp. 266. Copenhagen: 1928.

LEHRBUCH DER ALLGEMEINEN PATHOLOGIE UND DER PATHOLOGISCHEN ANATOMIE. Von Professor H. Ribbert. Neu bearbeitet von Dr. Carl Sternberg, Professor für pathologische Anatomie an der Universität in Wien. Paper. Price, 45 marks. Pp. 704, with 739 illustrations. Leipsig: F. C. W. Vogel, 1928.

This is, in the main, a new book. Most of the illustrations in Ribbert's lehrbuch have been retained. The book is a short but reliable and thorough introduction to the study of general pathology and pathologic anatomy from the morphologic point of view. To save space, the references to the literature are confined to large handbooks only.

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